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(54) **OXINDOLOPYRIMIDINE AS IGF1R RECEPTOR INHIBITORS**

OXINDOLOPYRIMIDINE ALS IGF1R REZEPTOR INHIBITOREN

DÉRIVÉS D'OXINDOLOPYRIMIDINE EN TANT QU'INHIBITEURS DU RÉCEPTEUR IGF1R

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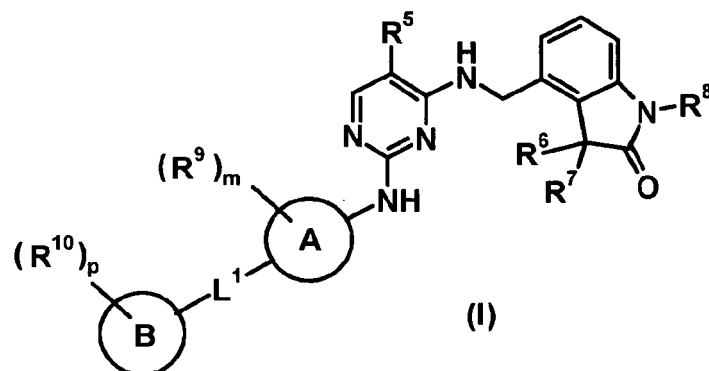
(56) References cited:

**WO-A1-2005/111022 WO-A2-2004/056786**  
**WO-A2-2007/081978**

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## Description

[0001] The present invention relates to new benzylic oxindolepyrimidines of general formula (I)



wherein the groups  $R^5$  to  $R^{10}$ ,  $A$ ,  $L^1$ ,  $B$ ,  $m$  and  $p$  have the meanings given in the claims and specification, which are suitable for the treatment of diseases characterised by excessive or abnormal cell proliferation, pharmaceutical preparations which contain such compounds and their use as medicaments. The compounds according to the invention display an inhibitory effect on the phosphorylation activity of the IGF-1 receptor located in cell membranes.

## Background to the invention

[0002] WO 2006/021544 describes diamino-substituted pyrimidines that carry bi- and tricyclic substituents in position 4 of the pyrimidine ring, as PLK1 inhibitors.

[0003] WO 2004/080980 describes diamino-substituted pyrimidines that carry *inter alia* bicyclic substituents in position 4 of the pyrimidine ring, as IGF-1 R inhibitors.

[0004] The aim of the present invention is to indicate new compounds which can be used for the prevention and/or treatment of diseases characterised by excessive or abnormal cell proliferation. The compounds according to the invention are characterised by a powerful inhibitory effect on the phosphorylation activity of the IGF-1 receptor located in cell membranes and a potent efficacy against tumour cells, e.g. glioblastoma cells, which is mediated through the inhibition of phosphorylation of the receptor. In addition to the inhibitory effect and cell activity the compounds have good solubility and good PK properties and good selectivity over other kinases (Invitrogen panel).

[0005] The insulin-like growth factor (IGF) and insulin signalling network is a highly conserved and essential pathway involved in biological processes including growth, metabolism and homeostasis. In addition, deregulated signalling via this network can enhance tumorigenesis and metastasis of certain cancers.

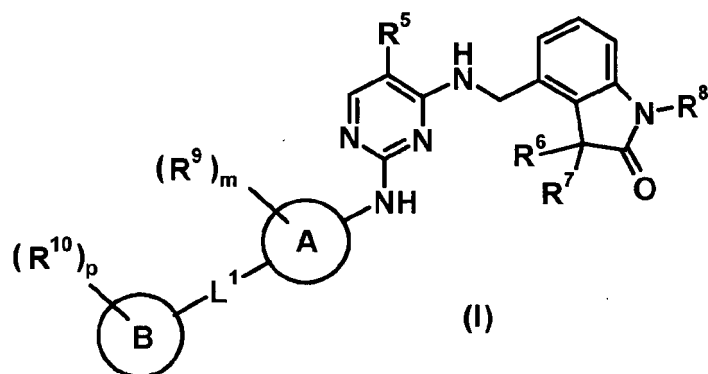
[0006] The ligands IGF-1, IGF-2 and insulin are highly homologous and activate specific hetero or homodimers of the IGF-1R and IR. Following ligand binding, the IGF-1R and IR undergo autophosphorylation mediated via the receptor tyrosine kinase domains. The phosphorylated receptors activate the canonical Ras-Raf-MEK-ERK1/2 and PI3K- PDK1-Akt intracellular signaling cascades, which leads to cell proliferation and survival. In addition, activation of the IR by insulin stimulates the uptake of glucose and storage of glycogen in metabolic tissues such as the liver, adipose and muscle.

[0007] Published research articles as well as medical and epidemiological investigations have identified a strong correlation between expression of the IGF-1R and IR and ligands for these receptors in tumor development and progression. Developing a small molecule competitive inhibitor of the ATP-binding pocket of the IGF-1R and IR as a means of blocking growth and survival signaling cascades in cancer is therefore desirable. The anticipated clinical benefit of blocking such an interaction would be to reduce tumor growth rate and potentially sensitize tumors to cytotoxic agents or targeted therapies.

## Detailed description of the invention

[0008] Surprisingly it has been found that compounds of general formula (I), wherein the groups  $R^5$  to  $R^{10}$ ,  $A$ ,  $L^1$ ,  $B$ ,  $m$  and  $p$  have the meanings stated hereinafter, act as inhibitors of receptors that are involved in controlling cell proliferation. Thus, the compounds according to the invention may be used for example for the treatment of diseases associated with the activity of these receptors and characterised by excessive or abnormal cell proliferation.

[0009] The present invention therefore relates to compounds of general formula (I)



wherein

**(A0)**

$R^5$  is selected from among trifluoromethyl and halogen;

**(B0)**

$R^6$ ,  $R^7$  and  $R^8$  are each independently selected from among hydrogen and  $C_{1-4}$ alkyl or  $R^6$  and  $R^7$  together with the carbon atom to which they bond form a saturated, 3-5 membered hydrocarbon ring;

**(C0)**

ring system **A** is selected from among  $C_{6-10}$ aryl, 3-14 membered heterocyclyl and 5-12 membered heteroaryl;

**(D0)**

each  $R^9$  is independently selected in each case from among  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ haloalkoxy, halogen and -CN;

$m$  denotes 0, 1, 2 or 3;

**(E0)**

$L^1$  is selected from among a bond,  $-(CH_2)_n-O$ ,  $-(CH_2)_n-NH$ ,  $-(CH_2)_n-NH-C(O)$ ,  $-(CH_2)_n-C(O)-NH$ ,  $-(CH_2)_n-$  and  $-(CH_2)_n-C(O)$ , while in the present nomenclature the linker group  $L^1$  on the right binds to the ring system **A**;

$n$  denotes 0, 1, 2 or 3;

**(F0)**

ring system **B** is selected from among 4-10 membered, saturated or unsaturated heterocyclyl and phenyl;

**(G0)**

each  $R^{10}$  is independently selected in each case from among  $R^a$  and  $R^b$ ;

$p$  denotes 0, 1, 2 or 3;

each  $R^a$  independently denotes a group optionally substituted by one or more identical or different  $R^b$  and/or  $R^c$  selected from among  $C_{1-a}$ alkyl,  $C_{2-a}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl; each  $R^b$  is independently selected in each case from among  $-OR^c$ ,  $-SR^c$ ,  $-NR^cR^c$ , halogen, -CN,  $-NO_2$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-C(NR^f)NR^cR^c$ ,  $-OC(O)R^c$ ,  $-OC(O)OR^c$ ,  $-S(O)_2R^c$ ,  $-S(O)_2NR^cR^c$ ,  $-NR^fC(O)R^c$ ,  $-NR^fC(O)OR^c$ ,  $-NR^fC(O)NR^cR^c$ ,  $-NR^fC(NR)NR^cR^c$  and  $-NR^fS(O)_2R^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each  $R^c$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^d$  and/or  $R^e$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

each  $R^d$  is independently selected in each case from among  $-OR^e$ ,  $-SR^e$ ,  $-NR^eR^e$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$ ,  $-C(O)NR^eR^e$ ,  $-C(NR^f)NR^eR^e$ ,  $-OC(O)R^e$ ,  $-OC(O)OR^e$ ,  $-S(O)_2R^e$ ,  $-S(O)_2NR^eR^e$ ,  $-NR^fC(O)R^e$ ,  $-NR^fC(O)OR^e$ ,  $-NR^fC(O)NR^eR^e$ ,  $-NR^fC(NR^f)NR^eR^e$  and  $-NR^fS(O)_2R^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

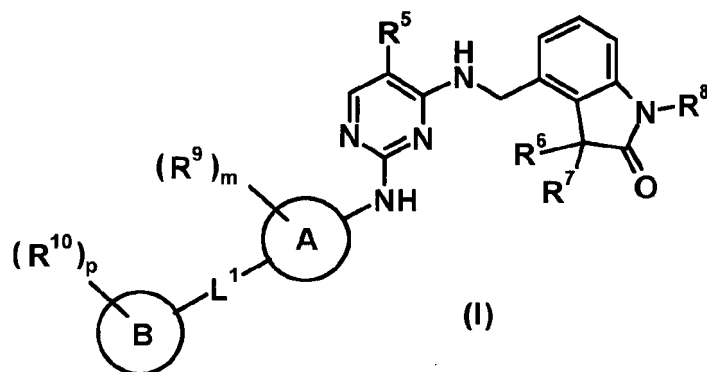
each  $R^e$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^f$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl, and

each  $R^f$  is independently selected in each case from among hydrogen and  $C_{1-6}$ alkyl,

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while the compounds (I) may optionally also occur in the form of their tautomers, racemates, enantiomers, diastereomers or mixtures thereof, or as the respective salts of all the above-mentioned forms.

**[0010]** The present invention further relates to compounds of general formula (I)



wherein

(A0)

$R^5$  is selected from among trifluoromethyl and halogen;

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(B0)

$R^6$ ,  $R^7$  and  $R^8$  are independently selected in each case from among hydrogen and  $C_{1-4}$ alkyl or  $R^6$  and  $R^7$  together with the carbon atom to which they bond forms a saturated, 3-5 membered hydrocarbon ring;

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(C0)

ring system A is selected from among  $C_{6-10}$ aryl and 5-12 membered heteroaryl;

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(D0)

each  $R^9$  is independently selected in each case from among  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, halogen and  $-CN$ ;

$m$  denotes 0, 1, 2 or 3;

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(E0)

$L^1$  is selected from among a bond,  $-(CH_2)_n-O$ ,  $-(CH_2)_n-NH$ ,  $-(CH_2)_n-NH-C(O)$ ,  $-(CH_2)_n-C(O)-NH$ ,  $-(CH_2)_n-$  and  $-(CH_2)_n-C(O)$ , while in the present nomenclature the linker group  $L^1$  on the right binds to the ring system A;

$n$  denotes 0, 1, 2 or 3;

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(F0)

ring system B is selected from among 4-10 membered, saturated or unsaturated heterocyclyl and phenyl;

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(G0)

each **R<sup>10</sup>** is independently selected in each case from among **R<sup>a</sup>** and **R<sup>b</sup>**;  
**p** denotes 0, 1, 2 or 3;

each **R<sup>a</sup>** independently denotes a group optionally substituted by one or more identical or different **R<sup>b</sup>** and/or **R<sup>c</sup>** selected from among C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-10</sub>cycloalkyl, C<sub>4-10</sub>cycloalkenyl, C<sub>6-10</sub>aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

each **R<sup>b</sup>** is independently selected in each case from among -OR<sup>c</sup>, -SR<sup>c</sup>, -NR<sup>c</sup>R<sup>c</sup>, halogen, -CN, -NO<sub>2</sub>, -C(O)R<sup>c</sup>, -C(O)OR<sup>c</sup>, -C(O)NR<sup>c</sup>R<sup>c</sup>, -C(NR<sup>f</sup>)NR<sup>c</sup>R<sup>c</sup>, -OC(O)R<sup>c</sup>, -OC(O)OR<sup>c</sup>, -S(O)<sub>2</sub>R<sup>c</sup>, -S(O)<sub>2</sub>NR<sup>c</sup>R<sup>c</sup>, -NR<sup>f</sup>C(O)R<sup>c</sup>, -NR<sup>f</sup>C(O)OR<sup>c</sup>, -NR<sup>f</sup>C(O)NR<sup>c</sup>R<sup>c</sup>, -NR<sup>f</sup>C(NR<sup>f</sup>)NR<sup>c</sup>R<sup>c</sup> and -NR<sup>f</sup>S(O)<sub>2</sub>R<sup>c</sup>, as well as the bivalent substituent =O, while the latter may only be a substituent in non-aromatic ring systems;

each **R<sup>c</sup>** independently denotes hydrogen or a group optionally substituted by one or more identical or different **R<sup>d</sup>** and/or **R<sup>e</sup>** selected from among C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-10</sub>cycloalkyl, C<sub>4-10</sub>cycloalkenyl, C<sub>6-10</sub>aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

each **R<sup>d</sup>** is independently selected in each case from among -OR<sup>e</sup>, -SR<sup>e</sup>, -NR<sup>e</sup>R<sup>e</sup>, halogen, -CN, -NO<sub>2</sub>, -C(O)R<sup>e</sup>, -C(O)OR<sup>e</sup>, -C(O)NR<sup>e</sup>R<sup>e</sup>, -C(NR<sup>f</sup>)NR<sup>e</sup>R<sup>e</sup>, -OC(O)R<sup>e</sup>, -OC(O)OR<sup>e</sup>, -S(O)<sub>2</sub>R<sup>e</sup>, -S(O)<sub>2</sub>NR<sup>e</sup>R<sup>e</sup>, -NR<sup>f</sup>C(O)R<sup>e</sup>, -NR<sup>f</sup>C(O)OR<sup>e</sup>, -NR<sup>f</sup>C(O)NR<sup>e</sup>R<sup>e</sup>, -NR<sup>f</sup>C(NR<sup>f</sup>)NR<sup>e</sup>R<sup>e</sup> and -NR<sup>f</sup>S(O)<sub>2</sub>R<sup>e</sup>, as well as the bivalent substituent =O, while the latter may only be a substituent in non-aromatic ring systems;

each **R<sup>e</sup>** independently denotes hydrogen or a group optionally substituted by one or more identical or different **R<sup>f</sup>** selected from among C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-10</sub>cycloalkyl, C<sub>4-10</sub>cycloalkenyl, C<sub>6-10</sub>aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl, and

each **R<sup>f</sup>** is independently selected in each case from among hydrogen and C<sub>1-6</sub>alkyl,

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while the compounds (**I**) may optionally also occur in the form of their tautomers, racemates, enantiomers, diastereomers or mixtures thereof, or as the respective salts of all the above-mentioned forms.

**[0011]** In one aspect (**A1**) the invention relates to compounds (**I**), wherein **R<sup>5</sup>** denotes trifluoromethyl.

**[0012]** In one aspect (**A2**) the invention relates to compounds (**I**), wherein **R<sup>5</sup>** denotes chlorine.

**[0013]** In one aspect (**A3**) the invention relates to compounds (**I**), wherein **R<sup>5</sup>** denotes bromine.

**[0014]** In another aspect (**B1**) the invention relates to compounds (**I**), wherein **R<sup>6</sup>** and **R<sup>7</sup>** in each case denote methyl and **R<sup>8</sup>** denotes hydrogen.

**[0015]** In another aspect (**B2**) the invention relates to compounds (**I**), wherein **R<sup>6</sup>**, **R<sup>7</sup>** and **R<sup>8</sup>** in each case denote hydrogen.

**[0016]** In another aspect (**B3**) the invention relates to compounds (**I**), wherein **R<sup>6</sup>** and **R<sup>7</sup>** together with the carbon atom to which they bond form a cyclopropyl ring and **R<sup>8</sup>** denotes hydrogen.

**[0017]** In another aspect (**C1**) the invention relates to compounds (**I**), wherein ring system **A** is selected from among phenyl and 5-6 membered heteroaryl.

**[0018]** In another aspect (**C2**) the invention relates to compounds (**I**), wherein ring system **A** is a phenyl.

**[0019]** In another aspect (**C3**) the invention relates to compounds (**I**), wherein ring system **A** is a 5-6 membered, nitrogen-containing heteroaryl.

**[0020]** In another aspect (**C4**) the invention relates to compounds (**I**), wherein ring system **A** is a pyridyl or pyrazolyl;

**[0021]** In another aspect (**D1**) the invention relates to compounds (**I**) wherein **m** has the value 0.

**[0022]** In another aspect (**D2**) the invention relates to compounds (**I**), wherein **m** has the value 1 or 2 and

**R<sup>9</sup>** is selected from among halogen, C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy.

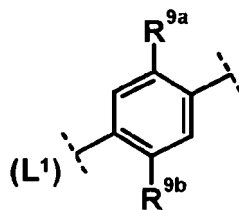
**[0023]** In another aspect (**D3**) the invention relates to compounds (**I**), wherein **m** has the value 1 or 2 and

**R<sup>9</sup>** is selected from among C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy.

**[0024]** In another aspect (**D4**) the invention relates to compounds (**I**), wherein **m** has the value 1 or 2 and

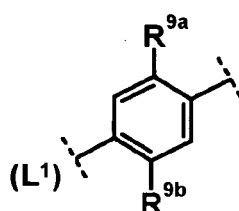
**R<sup>9</sup>** is selected from among methyl, ethyl, methoxy and ethoxy.

**[0025]** In another aspect (**CD1**) the invention relates to compounds (**I**), wherein ring system **A** and the **m** groups **R<sup>9</sup>** together denote



$R^{9a}$  is selected from among hydrogen,  $C_{1-4}$ alkyl and  $C_{1-4}$ alkoxy and  $R^{9b}$  is selected from among hydrogen and  $C_{1-4}$ alkyl.

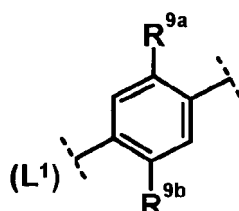
[0026] In another aspect (CD2) the invention relates to compounds (I), wherein ring system **A** and the m groups  $R^9$  together denote



$R^{9a}$  is selected from among  $C_{1-4}$ alkyl and  $C_{1-4}$ alkoxy and

$R^{9b}$  is selected from among hydrogen and  $C_{1-4}$ alkyl.

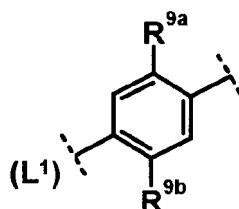
[0027] In another aspect (CD3) the invention relates to compounds (I), wherein ring system **A** and the m groups  $R^9$  together denote



$R^{9a}$  is selected from among hydrogen, methyl, ethyl, methoxy and ethoxy and

$R^{9b}$  is selected from among hydrogen, methyl and ethyl.

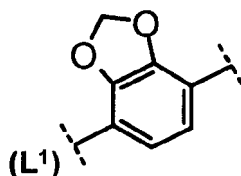
[0028] In another aspect (CD4) the invention relates to compounds (I), wherein ring system **A** and the m groups  $R^9$  together denote



$R^{9a}$  is selected from among methyl, ethyl, methoxy and ethoxy and

$R^{9b}$  is selected from among hydrogen, methyl and ethyl.

[0029] In another aspect (CD5) the invention relates to compounds (I), wherein ring system **A** and the m groups  $R^9$  together denote



In another aspect (**E1**) the invention relates to compounds (**I**), wherein

**L¹** is selected from among a bond,  $-(CH_2)_2-O$ ,  $-NH-C(O)$ ,  $-C(O)-NH-$  and  $-C(O)$ , while in the present nomenclature the linker group **L¹** on the right binds to the ring system **A**.

**[0030]** In another aspect (**E2**) the invention relates to compounds (**I**), wherein **L¹** corresponds to a bond.

**[0031]** In another aspect (**E3**) the invention relates to compounds (**I**), wherein **L¹** is selected from among  $-(CH_2)_2-O$ ,  $-NH-C(O)-$  and  $-C(O)-$ .

**[0032]** In another aspect (**F1**) the invention relates to compounds (**I**), wherein ring system **B** is a 4-10 membered, saturated or unsaturated heterocyclyl.

**[0033]** In another aspect (**F2**) the invention relates to compounds (**I**), wherein ring system **B** is a 5-7 membered, saturated and nitrogen-containing heterocyclyl.

**[0034]** In another aspect (**F3**) the invention relates to compounds (**I**), wherein ring system **B** is selected from among piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and 2,5-diaza-bicyclo[2,2,1]heptyl.

**[0035]** In another aspect (**G1**) the invention relates to compounds (**I**), wherein **p** has the value 0.

**[0036]** In another aspect (**G2**) the invention relates to compounds (**I**), wherein **p** has the value 1 or 2;

each **R¹⁰** is independently selected in each case from among **Rᵃ** and **Rᵇ**;

each **Rᵃ** independently denotes a group optionally substituted by one or more identical or different **Rᵇ** and/or **Rᶜ** selected from among C<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl and 3-14 membered heterocyclyl;

each **Rᵇ** is independently selected in each case from among  $-OR^c$ ,  $-NR^cR^c$ , halogen,  $-CN$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-S(O)_2R^c$  and  $-S(O)_2NR^cR^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each **Rᶜ** independently denotes hydrogen or a group optionally substituted by one or more identical or different **Rᵈ** and/or **Rᵉ** selected from among C<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

each **Rᵈ** is independently selected in each case from among  $-OR^e$ ,  $-NR^eR^e$ ,  $-CN$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$  and  $-NR^fC(O)OR^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each **Rᵉ** independently denotes hydrogen or a group optionally substituted by one or more identical or different **Rᶜ** selected from among C<sub>1-6</sub>alkyl, C<sub>6-10</sub>aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl, and

each **Rᶜ** is independently selected in each case from among hydrogen and C<sub>1-6</sub>alkyl.

**[0037]** In another aspect (**G3**) the invention relates to compounds (**I**), wherein **p** has the value 1 or 2,

each **R¹⁰** is independently selected in each case from among **Rᵃ** and **Rᵇ**;

each **Rᵃ** independently denotes a group optionally substituted by one or more identical or different **Rᵇ** and/or **Rᶜ** selected from among C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl and 4-7 membered heterocyclyl;

each **Rᵇ** is independently selected in each case from among  $-OR^c$ ,  $-NR^cR^c$ , halogen,  $-CN$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-S(O)_2R^c$  and  $-S(O)_2NR^cR^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

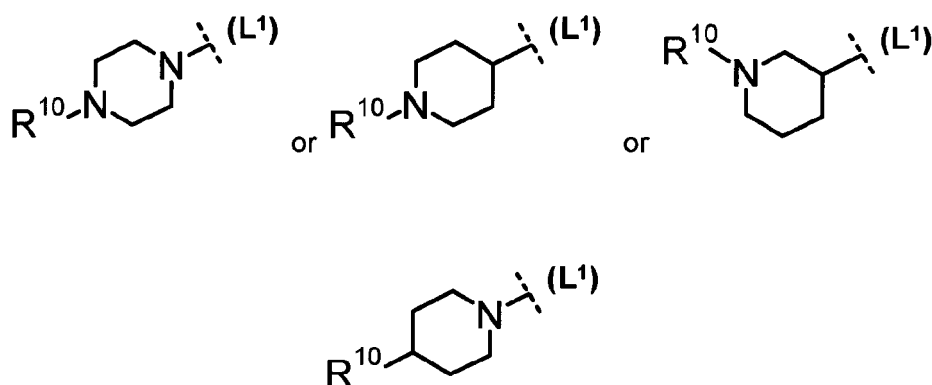
each **Rᶜ** independently denotes hydrogen or a group optionally substituted by one or more identical or different **Rᵈ** and/or **Rᵉ** selected from among C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, 5-6 membered heteroaryl and 4-7 membered heterocyclyl;

each **Rᵈ** is independently selected in each case from among  $-OR^e$ ,  $-NR^eR^e$ ,  $-CN$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$  and  $-NR^fC(O)OR^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each **Rᵉ** independently denotes hydrogen or a group optionally substituted by one or more identical or different **Rᶜ** selected from among C<sub>1-6</sub>alkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocyclyl, and

each **Rᶜ** is independently selected in each case from among hydrogen and C<sub>1-6</sub>alkyl.

**[0038]** In another aspect (**FG1**) the invention relates to compounds (**I**), wherein ring system **B** and the **p** groups **R¹⁰** together denote



15 each  $R^{10}$  is independently selected in each case from among  $R^a$  and  $R^b$ ;

each  $R^a$  independently denotes a group optionally substituted by one or more identical or different  $R^b$  and/or  $R^c$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

each  $R^b$  is independently selected in each case from among  $-OR^c$ ,  $-SR^c$ ,  $-NR^cR^c$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-C(NR^f)NR^cR^c$ ,  $-OC(O)R^c$ ,  $-OC(O)OR^c$ ,  $-S(O)_2R^c$ ,  $-S(O)_2NR^cR^c$ ,  $-NR^fC(O)R^c$ ,  $-NR^fC(O)OR^c$ ,  $-NR^fC(O)NR^cR^c$ ,  $-NR^fC(NR^f)NR^cR^c$  and  $-NR^fS(O)_2R^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

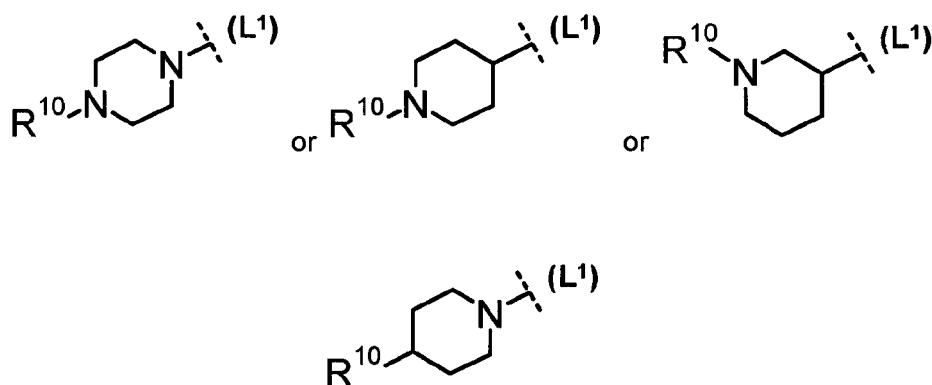
each  $R^c$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^d$  and/or  $R^e$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

each  $R^d$  is independently selected in each case from among  $-OR^e$ ,  $-SR^e$ ,  $-NR^eR^e$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$ ,  $-C(O)NR^eR^e$ ,  $-C(NR^f)NR^eR^e$ ,  $-OC(O)R^e$ ,  $-OC(O)OR^e$ ,  $-S(O)_2R^e$ ,  $-S(O)_2NR^eR^e$ ,  $-NR^fC(O)R^e$ ,  $-NR^fC(O)OR^e$ ,  $-NR^fC(O)NR^eR^e$ ,  $-NR^fC(NR^f)NR^eR^e$  and  $-NR^fS(O)_2R^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each  $R^e$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^f$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl, and

each  $R^f$  is independently selected in each case from among hydrogen and  $C_{1-6}$ alkyl.

[0039] In another aspect (FG2) the invention relates to compounds (II), wherein ring system B and the p groups  $R^{10}$  together denote



50 each  $R^{10}$  is independently selected in each case from among  $R^a$  and  $R^b$ ;

each  $R^a$  independently denotes a group optionally substituted by one or more identical or different  $R^b$  and/or  $R^c$  selected from among  $C_{1-6}$ alkyl,  $C_{3-10}$ cycloalkyl and 3-14 membered heterocyclyl;

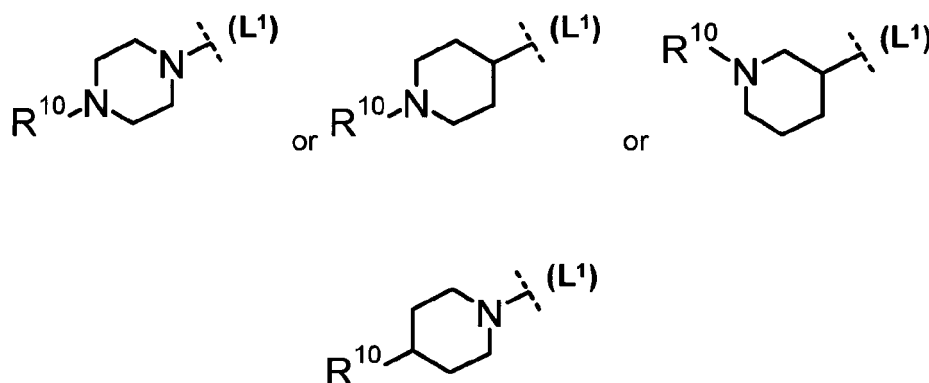
each  $R^b$  is independently selected in each case from among  $-OR^c$ ,  $-NR^cR^c$ , halogen,  $-CN$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-S(O)_2R^c$  and  $-S(O)_2NR^cR^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each  $R^c$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^d$  and/or  $R^e$  selected from among  $C_{1-6}$ alkyl,  $C_{3-10}$ cycloalkyl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;



each  $R^d$  is independently selected in each case from among  $-OR^e$ ,  $-NR^eR^e$ ,  $-CN$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$  and  $-NR^fC(O)OR^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems; each  $R^e$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^f$  selected from among  $C_{1-6}$ alkyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl, and each  $R^f$  is independently selected in each case from among hydrogen and  $C_{1-6}$ alkyl.

[0040] In another aspect (FG3) the invention relates to compounds (I), wherein ring system B and the p groups  $R^{10}$  together denote



each  $R^{10}$  is independently selected in each case from among  $R^a$  and  $R^b$ ;

each  $R^a$  independently denotes a group optionally substituted by one or more identical or different  $R^b$  and/or  $R^c$  selected from among  $C_{1-6}$ alkyl,  $C_{3-6}$ cycloalkyl and 4-7 membered heterocyclyl;

each  $R^b$  is independently selected in each case from among  $-OR^c$ ,  $-NR^cR^c$ , halogen,  $-CN$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-S(O)_2R^c$  and  $-S(O)_2NR^cR^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

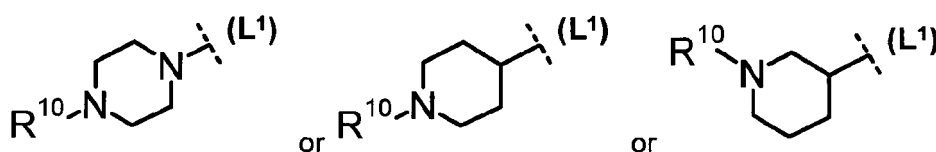
each  $R^c$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^d$  and/or  $R^e$  selected from among  $C_{1-6}$ alkyl,  $C_{3-6}$ cycloalkyl, 5-6 membered heteroaryl and 4-7 membered heterocyclyl;

each  $R^d$  is independently selected in each case from among  $-OR^e$ ,  $-NR^eR^e$ ,  $-CN$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$  and  $-NR^fC(O)OR^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each  $R^e$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^f$  selected from among  $C_{1-6}$ alkyl, phenyl, 5-6 membered heteroaryl and 4-7 membered heterocyclyl, and

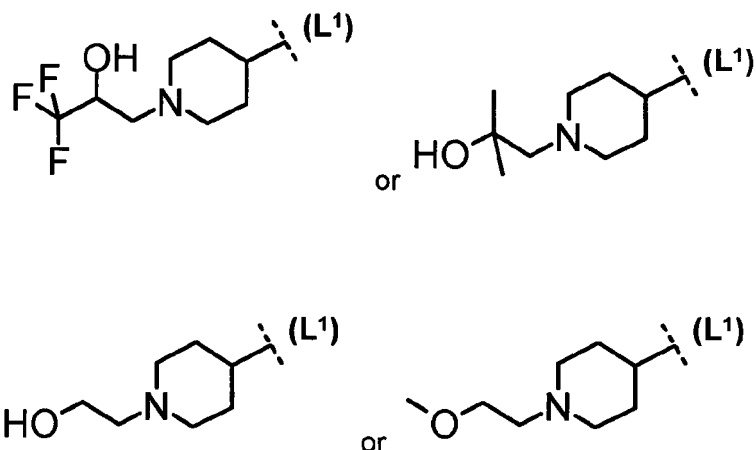
each  $R^f$  is independently selected in each case from among hydrogen and  $C_{1-6}$ alkyl.

[0041] In another aspect (FG4) the invention relates to compounds (I), wherein ring system B and the p groups  $R^{10}$  together denote

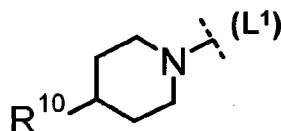


each  $R^{10}$  is independently selected in each case from among  $-C(O)-C_{1-4}$ alkyl, hydrogen,  $C_{1-6}$ alkyl (CN),  $C_{1-6}$ haloalkyl,  $-C(O)-O-C_{1-4}$ alkyl,  $-COOH$ ,  $(C_{1-4}alkyl)_2N-C_{1-4}alkylene-C(O)$ ,  $(C_{1-4}alkyl)NH-C_{1-4}alkylene-C(O)$ ,  $H_2N-C_{1-4}alkylene-C(O)$ ,  $HO-C_{1-4}alkylene-C(O)$ ,  $-C(O)-N(C_{1-4}alkyl)_2$ ,  $-C(O)-NH(C_{1-4}alkyl)$ ,  $-C(O)NH_2$ ,  $C_{1-4}alkyl-O-C_{1-4}alkylene-C(O)$ , 4-6 membered heterocyclyl (optionally substituted by  $C_{1-4}$ alkyl,  $C_{3-6}$ cycloalkyl or 3-6 membered heterocyclyl),  $C_{3-6}$ cycloalkyl,  $C_{3-6}$ cycloalkyl- $C_{1-4}$ alkyl,  $HO-C_{2-4}alkyl$ ,  $C_{1-4}alkyl-O-C_{2-4}alkyl$ ,  $HO-C_{2-4}haloalkyl$ ,  $C_{1-4}alkyl-S(O)_2$ ,  $C_{1-4}alkyl-NH-C(O)-C_{1-4}alkyl$ ,  $H_2N-C(O)-C_{1-4}alkyl$  and  $C_{1-4}alkyl-S(O)_2-C_{1-4}alkyl$

[0042] In another aspect (FG5) the invention relates to compounds (I), wherein ring system B and the p groups  $R^{10}$  together denote



**[0043]** In another aspect (**FG6**) the invention relates to compounds (**I**), wherein ring system **B** and the p groups **R<sup>10</sup>** together denote



each **R<sup>10</sup>** is independently selected in each case from among C<sub>1-4</sub>alkyl-O-C<sub>2-4</sub>alkylene-NH, C<sub>1-4</sub>alkyl-O-C<sub>2-4</sub>alkylene-N(C<sub>1-4</sub>alkyl), HO-C<sub>2-4</sub>alkylene-N(C<sub>1-4</sub>alkyl), HO-C<sub>2-4</sub>alkylene-NH, 4-6 membered heterocyclyl (optionally substituted by C<sub>1-4</sub>alkyl, 3-6 membered heterocyclyl, halogen, -OH, -CN, C<sub>1-4</sub>alkoxy, -N(C<sub>1-4</sub>alkyl)<sub>2</sub> or C<sub>3-6</sub>cycloalkyl), (C<sub>1-4</sub>alkyl)<sub>2</sub>N-C<sub>2-4</sub>alkylene-N(C<sub>1-4</sub>alkyl), (C<sub>1-4</sub>alkyl)<sub>2</sub>N-C<sub>2-4</sub>alkylene-NH, -N(C<sub>1-4</sub>alkyl)<sub>2</sub>, -NH(C<sub>1-4</sub>alkyl), C<sub>1-4</sub>alkyl-NH-C(O)- and (C<sub>1-4</sub>alkyl)<sub>2</sub>N-C(O).

**[0044]** In another aspect the invention relates to compounds (**I**), wherein **p** has the value 1.

**[0045]** All the above-mentioned structural aspects **A1** to **A3**, **B1** to **B3**, **C1** to **C4**, **D1** to **D4**, **CD1** to **CD5**, **E1** to **E3**, **F1** to **F3**, **G1** to **G3** and **FG1** to **FG6** are preferred embodiments of the respective aspects **A0**, **B0**, **C0**, **D0**, **CD0**, **E0**, **F0**, **G0** and **FG0**, wherein **CD0** denotes the combination of **C0** and **D0** and **FG0** denotes the combination of **F0** and **G0**. The structural aspects **A0** to **A3**, **B0** to **B3**, **C0** to **C4**, **D0** to **D4**, **CD0** to **CD5**, **E0** to **E3**, **F0** to **F3**, **G0** to **G3** and **FG0** to **FG6** with respect to different molecular parts of the compounds (**I**) according to the invention may be permuted with one another as desired to form **ABCDEFG** combinations, thus obtaining preferred compounds (**I**). Each **ABCDEFG** combination represents and defines individual embodiments or generic partial amounts of compounds **A0B0C0D0E0F0G0** according to the invention. Every individual embodiment or partial quantity defined by this combination is expressly included in and a subject of the invention.

**[0046]** The present disclosure further relates to hydrates, solvates, polymorphs, metabolites, derivatives and prodrugs of compounds of general formula (**I**).

**[0047]** The present invention further relates to a pharmaceutically acceptable salt of a compound of general formula (**I**) with an inorganic or organic acids or bases.

**[0048]** In another aspect the invention relates to compounds of general formula (**I**) - or the pharmaceutically acceptable salts thereof - as medicaments.

**[0049]** In another aspect the invention relates to compounds of general formula (**I**) - or the pharmaceutically acceptable salts thereof - for use in a method for treatment of the human or animal body.

**[0050]** In another aspect the invention relates to compounds of general formula (**I**) - or the pharmaceutically acceptable salts thereof - for use in the treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases.

**[0051]** In another aspect the invention relates to compounds of general formula (**I**) - or the pharmaceutically acceptable salts thereof - for use in a method for treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases in the human and animal body.

**[0052]** In another aspect the invention relates to the use of compounds of general formula (**I**) - or the pharmaceutically acceptable salts thereof - for preparing a pharmaceutical composition for the treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases.

**[0053]** In another aspect the invention relates to compounds of general formula (**I**) - or the pharmaceutically acceptable

salts thereof - for use in the treatment and/or prevention of cancer.

[0054] In another aspect the invention relates to the use of compounds of general formula (I) - or the pharmaceutically acceptable salts thereof - for preparing a pharmaceutical composition for the treatment and/or prevention of cancer.

[0055] In another aspect the invention relates to compounds of general formula (I) - or the pharmaceutically acceptable salts thereof - for use in a method for treatment and/or prevention of cancer in the human or animal body.

[0056] In another aspect the invention relates to compounds of general formula (I) - or the pharmaceutically acceptable salts thereof - for use in the treatment and/or prevention of hepatocellular carcinomas (HCC), non-small cell lung cancer (NSCLC), breast cancer and prostate cancer.

[0057] In another aspect the invention relates to the use of compounds of general formula (I) - or the pharmaceutically acceptable salts thereof - for preparing a pharmaceutical composition for the treatment and/or prevention of hepatocellular carcinomas (HCC), non-small cell lung cancer (NSCLC), breast cancer and prostate cancer.

[0058] In another aspect the invention relates to compounds of general formula (I) - or the pharmaceutically acceptable salts thereof - for use in the treatment and/or prevention of hepatocellular carcinomas (HCC) and non-small cell lung cancer (NSCLC).

[0059] In another aspect the invention relates to the use of compounds of general formula (I) - or the pharmaceutically acceptable salts thereof - for preparing a pharmaceutical composition for the treatment and/or prevention of hepatocellular carcinomas (HCC) and non-small cell lung cancer (NSCLC).

[0060] In another aspect the invention relates to a process for the treatment and/or prevention of cancer comprising administering a therapeutically effective amount of a compound of general formula (I) - or one of the pharmaceutically acceptable salts thereof - to a human being.

[0061] In another aspect the invention relates to a pharmaceutical preparation containing as active substance one or more compounds of general formula (I) - or the pharmaceutically acceptable salts thereof - optionally in combination with conventional excipients and/or carriers.

[0062] In another aspect the invention relates to a pharmaceutical preparation comprising a compound of general formula (I) - or one of the pharmaceutically acceptable salts thereof - and at least one other cytostatic or cytotoxic active substance, different from formula (I).

## Definitions

[0063] Terms that are not specifically defined here have the meanings that are apparent to the skilled man in the light of the overall disclosure and the context as a whole.

[0064] As used herein, the following definitions apply, unless stated otherwise:

The use of the prefix **C<sub>x-y</sub>**, wherein **x** and **y** each represent a natural number (**x** < **y**), indicates that the chains or ring structure or combination of chains and ring structure as a whole, specified and mentioned in direct association, may consist of a maximum of **y** and a minimum of **x** carbon atoms.

[0065] The indication of the number of members in groups that contain one or more heteroatom(s) (heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl) relates to the total atomic number of all the ring members or chain members or the total of all the ring and chain members.

[0066] **Alkyl** denotes monovalent, saturated hydrocarbon chains, which may be present in both straight-chain (unbranched) and branched form. If an **alkyl** is substituted, the substitution may take place independently of one another, by mono- or polysubstitution in each case, on all the hydrogen-carrying carbon atoms.

[0067] The term "**C<sub>1-5</sub>-alkyl**" includes for example H<sub>3</sub>C-, H<sub>3</sub>C-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, H<sub>3</sub>C-C(CH<sub>3</sub>)<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-, H<sub>3</sub>C-C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH(CH<sub>3</sub>)- and H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>2</sub>CH<sub>3</sub>)-.

[0068] Further examples of **alkyl** are methyl (Me; -CH<sub>3</sub>), ethyl (Et; -CH<sub>2</sub>CH<sub>3</sub>), 1-propyl (*n*-propyl; *n*-Pr; -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-propyl (*i*-Pr; *iso*-propyl; -CH(CH<sub>3</sub>)<sub>2</sub>), 1-butyl (*n*-butyl; *n*-Bu; -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-methyl-1-propyl (*iso*-butyl; *i*-Bu; -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2-butyl (*sec*-butyl; *sec*-Bu; -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 2-methyl-2-propyl (*tert*-butyl; *t*-Bu; -C(CH<sub>3</sub>)<sub>3</sub>), 1-pentyl (*n*-pentyl; -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-pentyl (-CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-pentyl (-CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3-methyl-1-butyl (*iso*-pentyl; -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2-methyl-2-butyl (-C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-methyl-2-butyl (-CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>), 2,2-dimethyl-1-propyl (*neo*-pentyl; -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 2-methyl-1-butyl (-CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 1-hexyl (*n*-hexyl; -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2-hexyl (-CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-hexyl (-CH(CH<sub>2</sub>CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)), 2-methyl-2-pentyl (-C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-methyl-2-pentyl (-CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 4-methyl-2-pentyl (-CH(CH<sub>3</sub>)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 3-methyl-3-pentyl (-C(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2-methyl-3-pentyl (-CH(CH<sub>2</sub>CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>), 2,3-dimethyl-2-butyl (-C(CH<sub>3</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 3,3-dimethyl-2-butyl (-CH(CH<sub>3</sub>)C(CH<sub>3</sub>)<sub>3</sub>), 2,3-dimethyl-1-butyl (-CH<sub>2</sub>CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)CH<sub>3</sub>), 2,2-dimethyl-1-butyl (-CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3,3-dimethyl-1-butyl (-CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 2-

methyl-1-pentyl (-CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3-methyl-1-pentyl (-CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 1-heptyl (*n*-heptyl), 2-methyl-1-hexyl, 3-methyl-1-hexyl, 2,2-dimethyl-1-pentyl, 2,3-dimethyl-1-pentyl, 2,4-dimethyl-1-pentyl, 3,3-dimethyl-1-pentyl, 2,2,3-trimethyl-1-butyl, 3-ethyl-1-pentyl, 1-octyl (*n*-octyl), 1-nonyl (*n*-nonyl); 1-decyl (*n*-decyl) etc.

[0069] By the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, wherein all isomeric forms are included.

[0070] The above definition for **alkyl** also applies if **alkyl** is a part of another group such as for example C<sub>x-y</sub>-**alkylamino** or C<sub>x-y</sub>-**alkyloxy**.

[0071] The term **alkylene** can also be derived from **alkyl**. **Alkylene** is bivalent, unlike **alkyl**, and requires two binding partners. Formally, the second valency is produced by removing a hydrogen atom in an **alkyl**. Corresponding groups are for example -CH<sub>3</sub> and -CH<sub>2</sub>, -CH<sub>2</sub>CH<sub>3</sub> and -CH<sub>2</sub>CH<sub>2</sub> or >CHCH<sub>3</sub> etc.

[0072] The term "**C<sub>1-4</sub>-alkylene**" includes for example -(CH<sub>2</sub>)-, -(CH<sub>2</sub>-CH<sub>2</sub>)-, -(CH(CH<sub>3</sub>))-, -(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>)-, -(C(CH<sub>3</sub>)<sub>2</sub>)-, -(CH(CH<sub>2</sub>CH<sub>3</sub>))-, -(CH(CH<sub>3</sub>)-CH<sub>2</sub>)-, -(CH<sub>2</sub>-CH(CH<sub>3</sub>))-, -(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>)-, -(CH<sub>2</sub>-CH<sub>2</sub>-CH(CH<sub>3</sub>))-, -(CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>)-, -(CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>)-, -(CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>)-, -(C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>)-, -(CH(CH<sub>3</sub>)-CH(CH<sub>3</sub>))-, -(CH<sub>2</sub>-CH(CH<sub>2</sub>CH<sub>3</sub>))-, -(CH(CH<sub>2</sub>CH<sub>3</sub>)-CH<sub>2</sub>)-, -(CH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>))-, -(CHCH(CH<sub>3</sub>)<sub>2</sub>)- and -C(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>)-.

[0073] Other examples of **alkylene** are methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene, hexylene etc.

[0074] By the generic terms propylene, butylene, pentylene, hexylene etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, *i.e.* propylene includes 1-methylethylene and butylene includes 1-methylpropylene, 2-methylpropylene, 1,1-dimethylethylene and 1,2-dimethylethylene. The above definition for **alkylene** also applies if **alkylene** is part of another group such as for example in HO-C<sub>x-y</sub>-**alkylenamino** or H<sub>2</sub>N-C<sub>x-y</sub>-**alkylenoxy**.

[0075] Unlike **alkyl**, **alkenyl** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C double bond. If in an **alkyl** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms on adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **alkenyl** is formed.

[0076] Examples of **alkenyl** are vinyl (ethenyl), prop-1-enyl, allyl (prop-2-enyl), isopropenyl, but-1-enyl, but-2-enyl, but-3-enyl, 2-methyl-prop-2-enyl, 2-methyl-prop-1-enyl, 1-methyl-prop-2-enyl, 1-methyl-prop-1-enyl, 1-methylidenepropyl, pent-1-enyl, pent-2-enyl, pent-3-enyl, pent-4-enyl, 3-methyl-but-3-enyl, 3-methyl-but-2-enyl, 3-methyl-but-1-enyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, hex-5-enyl, 2,3-dimethyl-but-3-enyl, 2,3-dimethyl-but-2-enyl, 2-methylidene-3-methylbutyl, 2,3-dimethyl-but-1-enyl, hexa-1,3-dienyl, hexa-1,4-dienyl, penta-1,4-dienyl, penta-1,3-dienyl, buta-1,3-dienyl, 2,3-dimethylbuta-1,3-diene etc.

[0077] By the generic terms propenyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, *i.e.* propenyl includes prop-1-enyl and prop-2-enyl, butenyl includes but-1-enyl, but-2-enyl, but-3-enyl, 1-methyl-prop-1-enyl, 1-methyl-prop-2-enyl etc.

[0078] **Alkenyl** may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

[0079] The above definition for **alkenyl** also applies when **alkenyl** is part of another group such as for example in C<sub>x-y</sub>-**alkenylamino** or C<sub>x-y</sub>-**alkenyloxy**.

[0080] Unlike **alkylene**, **alkenylene** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C double bond. If in an **alkylene** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms at adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **alkenylene** is formed.

[0081] Examples of **alkenylene** are ethenylene, propenylene, 1-methylethenylene, butenylene, 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene, pentenylene, 1,1-dimethylpropenylene, 2,2-dimethylpropenylene, 1,2-dimethylpropenylene, 1,3-dimethylpropenylene, hexenylene etc.

[0082] By the generic terms propenylene, butenylene, pentenylene, hexenylene etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, *i.e.* propenylene includes 1-methylethenylene and butenylene includes 1-methylpropenylene, 2-methylpropenylene, 1,1-dimethylethenylene and 1,2-dimethylethenylene.

[0083] **Alkenylene** may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

[0084] The above definition for **alkenylene** also applies when **alkenylene** is a part of another group as in for example HO-C<sub>x-y</sub>-**alkenylenamino** or H<sub>2</sub>N-C<sub>x-y</sub>-**alkenylenoxy**.

[0085] Unlike **alkyl**, **alkynyl** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C triple bond. If in an **alkyl** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding **alkynyl** is formed.

[0086] Examples of **alkynyl** are ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, 1-methyl-prop-2-

ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, 3-methyl-but-1-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl, hex-5-ynyl etc.

[0087] By the generic terms propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propynyl includes prop-1-ynyl and prop-2-ynyl, butynyl includes but-1-ynyl, but-2-ynyl, but-3-ynyl, 1-methyl-prop-1-ynyl, 1-methyl-prop-2-ynyl, etc.

[0088] If a hydrocarbon chain carries both at least one double bond and also at least one triple bond, by definition it belongs to the **alkynyl** subgroup.

[0089] The above definition for **alkynyl** also applies if **alkynyl** is part of another group, as in  $C_{x-y}$ -**alkynylamino** or  $C_{x-y}$ -**alkynyloxy**, for example.

[0090] Unlike **alkylene**, **alkynylene** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C triple bond. If in an **alkylene** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding **alkynylene** is formed.

[0091] Examples of **alkynylene** are ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2-dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene, hexynylene etc.

[0092] By the generic terms propynylene, butynylene, pentynylene, hexynylene etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propynylene includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 2-methylpropynylene, 1,1-dimethylethynylene and 1,2-dimethylethynylene.

[0093] The above definition for **alkynylene** also applies if **alkynylene** is part of another group, as in  $HO-C_{x-y}$ -**alkynyleneamino** or  $H_2N-C_{x-y}$ -**alkynyleneoxy**, for example.

[0094] By **heteroatoms** are meant oxygen, nitrogen and sulphur atoms.

[0095] **Haloalkyl (haloalkenyl, haloalkynyl)** is derived from the previously defined **alkyl (alkenyl, alkynyl)** by replacing one or more hydrogen atoms of the hydrocarbon chain independently of one another by halogen atoms, which may be identical or different. If a **haloalkyl (haloalkenyl, haloalkynyl)** is to be further substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms.

[0096] Examples of **haloalkyl (haloalkenyl, haloalkynyl)** are  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CF_2CF_3$ ,  $-CHFCH_2F$ ,  $-CH_2CF_3$ ,  $-CF_2CH_3$ ,  $-CHFCH_3$ ,  $-CF_2CF_2CF_3$ ,  $-CF_2CH_2CH_3$ ,  $-CF=CF_2$ ,  $-CCl=CH_2$ ,  $-CBr=CH_2$ ,  $-Cl=CH_2$ ,  $-C\equiv C-CF_3$ ,  $-CHFCH_2CH_3$ ,  $-CHFCH_2CF_3$  etc.

[0097] From the previously defined **haloalkyl (haloalkenyl, haloalkynyl)** are also derived the terms **haloalkylene (haloalkenylene, haloalkynylene)** **Haloalkylene (haloalkenyl, haloalkynyl)**, unlike **haloalkyl**, is bivalent and requires two binding partners. Formally, the second valency is formed by removing a hydrogen atom from a **haloalkyl**.

[0098] Corresponding groups are for example  $-CH_2F$  and  $-CHF-$ ,  $-CHFCH_2F$  and  $-CHFCHF-$  or  $>CFCH_2F$  etc.

[0099] The above definitions also apply if the corresponding halogen groups are part of another group.

[0100] **Halogen** relates to fluorine, chlorine, bromine and/or iodine atoms.

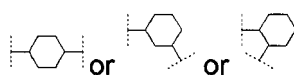
[0101] **Cycloalkyl** is made up of the subgroups **monocyclic hydrocarbon rings**, **bicyclic hydrocarbon rings** and **spiro-hydrocarbon rings**. The systems are saturated. In bicyclic hydrocarbon rings two rings are joined together so that they have at least two carbon atoms together. In spiro-hydrocarbon rings a carbon atom (spiroatom) belongs to two rings together. If a **cycloalkyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

[0102] Examples of **cycloalkyl** are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo-[4.3.0]nonyl (octahydroindenyl), bicyclo[4.4.0]decyl (decahydronaphthalene), bicyclo-[2.2.1]heptyl (norbornyl), bicyclo[4.1.0]heptyl (norcaranyl), bicyclo-[3.1.1]heptyl (pinanyl), spiro[2.5]octyl, spiro[3.3]heptyl etc.

[0103] The above definition for **cycloalkyl** also applies if **cycloalkyl** is part of another group as in  $C_{x-y}$ -**cycloalkylamino** or  $C_{x-y}$ -**cycloalkyloxy**, for example.

[0104] If the free valency of a **cycloalkyl** is saturated, then an **alicyclic group** is obtained.

[0105] The term **cycloalkylene** can thus be derived from the previously defined **cycloalkyl**. **Cycloalkylene**, unlike **cycloalkyl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **cycloalkyl**. Corresponding groups are for example cyclohexyl and



(cyclohexylene).

[0106] The above definition for **cycloalkylene** also applies if **cycloalkylene** is part of another group as in HO-C<sub>x-y</sub>-**cycloalkyleneamino** or H<sub>2</sub>N-C<sub>x-y</sub>-**cycloalkyleneoxy**, for example.

[0107] **Cycloalkenyl** is also made up of the subgroups **monocyclic hydrocarbon rings**, **bicyclic hydrocarbon rings** and **spiro-hydrocarbon rings**. However, the systems are unsaturated, i.e. there is at least one C-C double bond but no aromatic system. If in a **cycloalkyl** as hereinbefore defined two hydrogen atoms at adjacent cyclic carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **cycloalkenyl** is obtained. If a **cycloalkenyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkenyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

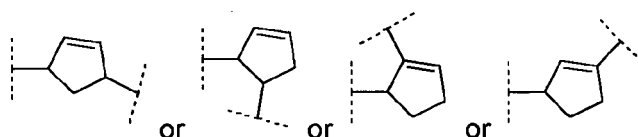
[0108] Examples of **cycloalkenyl** are cycloprop-1-enyl, cycloprop-2-enyl, cyclobut-1-enyl, cyclobut-2-enyl, cyclopent-1-enyl, cyclopent-2-enyl, cyclopent-3-enyl, cyclohex-1-enyl, cyclohex-2-enyl, cyclohex-3-enyl, cyclohept-1-enyl, cyclohept-2-enyl, cyclohept-3-enyl, cyclohept-4-enyl, cyclobuta-1,3-dienyl, cyclopenta-1,4-dienyl, cyclopenta-1,3-dienyl, cyclopenta-2,4-dienyl, cyclohexa-1,3-dienyl, cyclohexa-1,5-dienyl, cyclohexa-2,4-dienyl, cyclohexa-1,4-dienyl, cyclohexa-2,5-dienyl, bicyclo[2.2.1]hepta-2,5-dienyl (norborna-2,5-dienyl), bicyclo[2.2.1]hept-2-enyl (norbornenyl), spiro[4.5]dec-2-ene etc.

[0109] The above definition for **cycloalkenyl** also applies when **cycloalkenyl** is part of another group as in C<sub>x-y</sub>-**cycloalkenylamino** or C<sub>x-y</sub>-**cycloalkenylloxy**, for example.

[0110] If the free valency of a **cycloalkenyl** is saturated, then an **unsaturated alicyclic group** is obtained.

[0111] The term **cycloalkenylene** can thus be derived from the previously defined **cycloalkenyl**.

[0112] **Cycloalkenylene**, unlike **cycloalkenyl**, is bivalent and requires two binding partners. Formally the second valency is obtained by removing a hydrogen atom from a **cycloalkenyl**. Corresponding groups are for example cyclopentenyl and



(cyclopentenylene) etc.

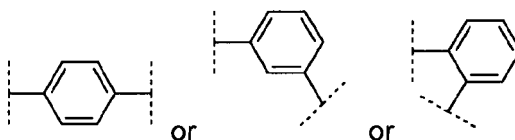
[0113] The above definition for **cycloalkenylene** also applies when **cycloalkenylene** is part of another group as in HO-C<sub>x-y</sub>-**cycloalkenyleneamino** or H<sub>2</sub>N-C<sub>x-y</sub>-**cycloalkenyleneoxy**, for example.

[0114] **Aryl** denotes a mono-, bi- or tricyclic group with at least one aromatic carbocycle. Preferably it denotes a monocyclic group with six carbon atoms (phenyl) or a bicyclic group with nine or ten carbon atoms (two six-membered rings or one six-membered ring with a five-membered ring), wherein the second ring may also be aromatic or, however, may also be saturated or partially saturated. If an **aryl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Aryl** itself may be linked as a substituent to the molecule via every suitable position of the ring system. Examples of **aryl** are phenyl, naphthyl, indanyl (2,3-dihydroindenyl), indenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl (1,2,3,4-tetrahydronaphthyl, tetralinyl), dihydronaphthyl (1,2-dihydronaphthyl), fluorenyl etc.

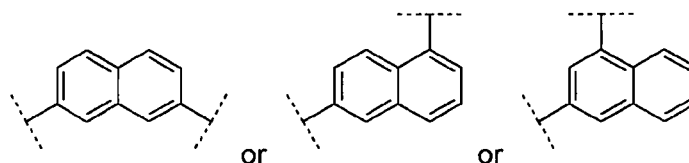
[0115] The above definition of **aryl** also applies when **aryl** is part of another group as in **arylamino** or **aryloxy**, for example.

[0116] If the free valency of an **aryl** is saturated, then an **aromatic group** is obtained.

[0117] The term **arylene** can also be derived from the previously defined **aryl**. **Arylene**, unlike **aryl**, is bivalent and requires two binding partners. Formally, the second valency is formed by removing a hydrogen atom from an **aryl**. Corresponding groups are e.g. phenyl and



(*o*, *m*, *p*-phenylene), naphthyl and



etc.

[0118] The above definition for **arylene** also applies when **arylene** is part of another group as in HO-**aryleneamino** or H<sub>2</sub>N-**aryleneoxy** for example.

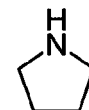
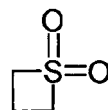
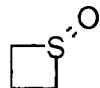
[0119] **Heterocyclyl** denotes ring systems, which are derived from the previously defined **cycloalkyl**, **cycloalkenyl** and **aryl** by replacing one or more of the groups -CH<sub>2</sub>- independently of one another in the hydrocarbon rings by the groups -O-, -S- or -NH- or by replacing one or more of the groups =CH- by the group =N-, wherein a total of not more than five heteroatoms may be present, at least one carbon atom may be present between two oxygen atoms and between two sulphur atoms or between one oxygen and one sulphur atom and the ring as a whole must have chemical stability. Heteroatoms may optionally be present in all the possible oxidation stages (sulphur → sulfoxide -SO-, sulphone -SO<sub>2</sub>-; nitrogen → N-oxide). In a **heterocyclyl** there is no heteroaromatic ring, i.e. no heteroatom is part of an aromatic system.

[0120] A direct result of the derivation from **cycloalkyl**, **cycloalkenyl** and **aryl** is that **heterocyclyl** is made up of the subgroups **monocyclic heterorings**, **bicyclic heterorings**, **tricyclic heterorings** and **spiro-heterorings**, which may be present in saturated or unsaturated form. By unsaturated is meant that there is at least one double bond in the ring system in question, but no heteroaromatic system is formed. In bicyclic heterorings two rings are linked together so that they have at least two (hetero)atoms in common. In spiro-heterorings a carbon atom (spiroatom) belongs to two rings together. If a **heterocyclyl** is substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. **Heterocyclyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

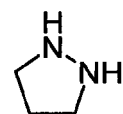
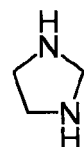
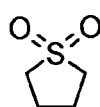
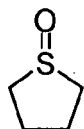
[0121] Examples of **heterocyclyl** are tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, thiazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, oxiranyl, aziridinyl, azetidiny, 1,4-dioxanyl, azepanyl, diazepanyl, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidinyl, homopiperazinyl, homothiomorpholinyl, thiomorpholinyl-S-oxide, thiomorpholinyl-S,S-dioxide, 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, [1,4]-oxazepanyl, tetrahydrothienyl, homothiomorpholinyl-S,S-dioxide, oxazolidinonyl, dihydro-pyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridyl, dihydro-pyrimidinyl, dihydro-furyl, dihydropyranyl, tetrahydrothienyl-S-oxide, tetrahydrothienyl-S,S-dioxide, homothiomorpholinyl-S-oxide, 2,3-dihydroazet, 2H-pyrrolyl, 4H-pyranyl, 1,4-dihydropyridinyl, 8-aza-bicyclo[3.2.1]octyl, 8-azabicyclo[5.1.0]octyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 2,5-diaza-bicyclo-[2.2.1]heptyl, 1-aza-bi-cyclo[2.2.2]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 3,9-diaza-bicyclo[4.2.1]nonyl, 2,6-diaza-bicyclo[3.2.2]nonyl, 1,4-dioxa-spiro[4.5]decyl, 1-oxa-3,8-diaza-spiro[4.5]decyl, 2,6-diaza-spiro[3.3]heptyl, 2,7-diaza-spiro[4.4]nonyl, 2,6-diaza-spiro[3.4]octyl, 3,9-diaza-spiro[5.5]undecyl, 2,8-diaza-spiro[4.5]decyl etc.

[0122] Further examples are the structures illustrated below, which may be attached via each hydrogen-carrying atom (exchanged for hydrogen):

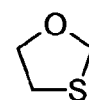
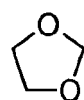
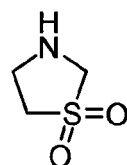
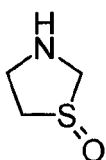
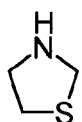
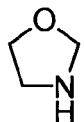
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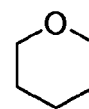
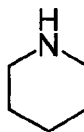
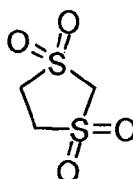
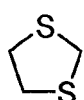
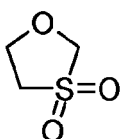
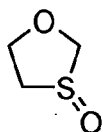
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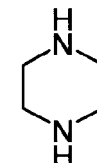
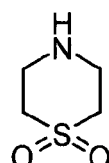
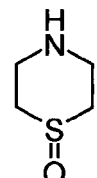
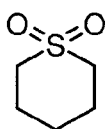
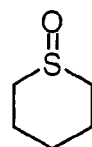
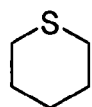
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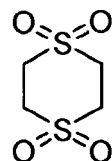
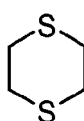
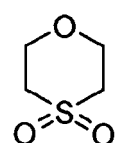
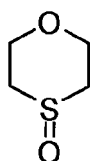
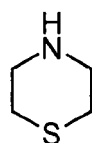
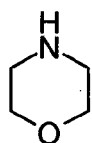
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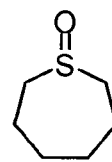
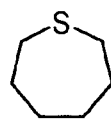
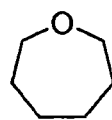
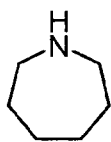
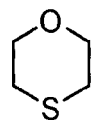
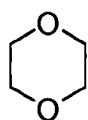
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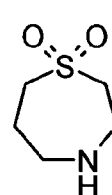
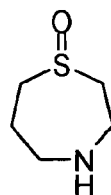
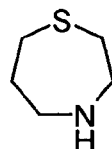
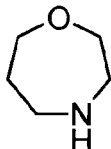
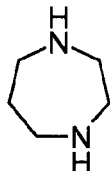
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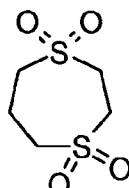
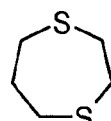
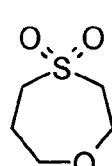
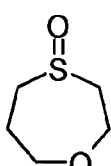
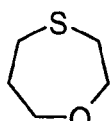
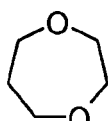
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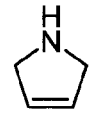
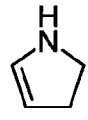
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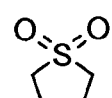
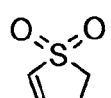
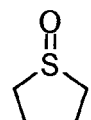
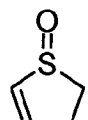
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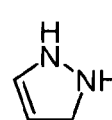
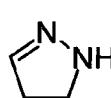
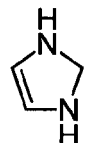
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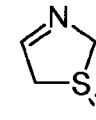
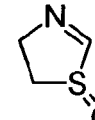
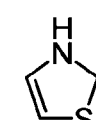
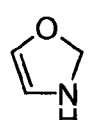
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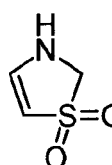
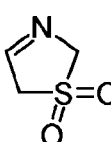
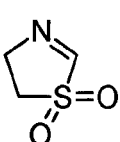
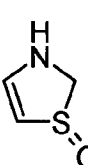
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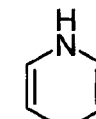
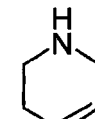
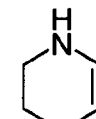
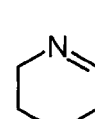
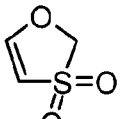
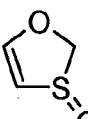
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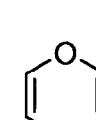
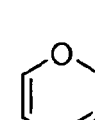
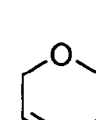
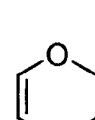
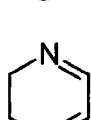
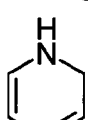
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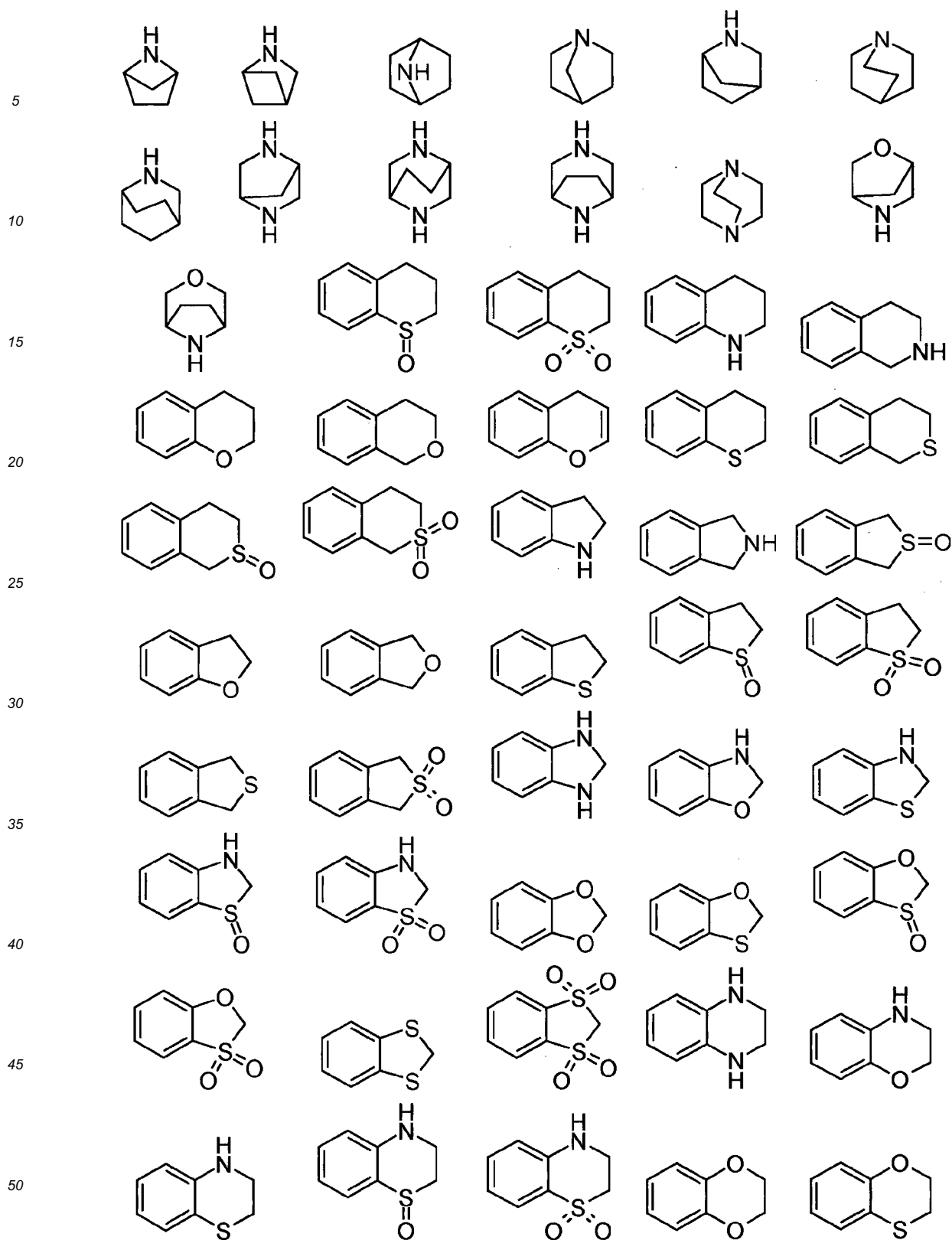
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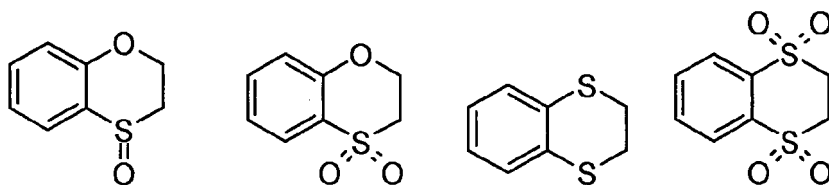


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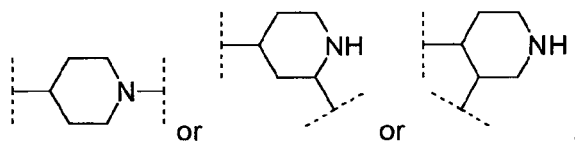
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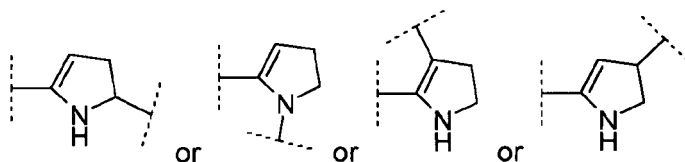


[0123] The above definition of **heterocyclyl** also applies if **heterocyclyl** is part of another group as in **heterocyclylamino** or **heterocyclyoxy** for example.

[0124] If the free valency of a **heterocyclyl** is saturated, then a **heterocyclic group** is obtained. The term **heterocyclylene** is also derived from the previously defined **heterocyclyl**. **Heterocyclylene**, unlike **heterocyclyl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **heterocyclyl**. Corresponding groups are for example piperidinyl and



2,3-dihydro-1H-pyrrolyl and



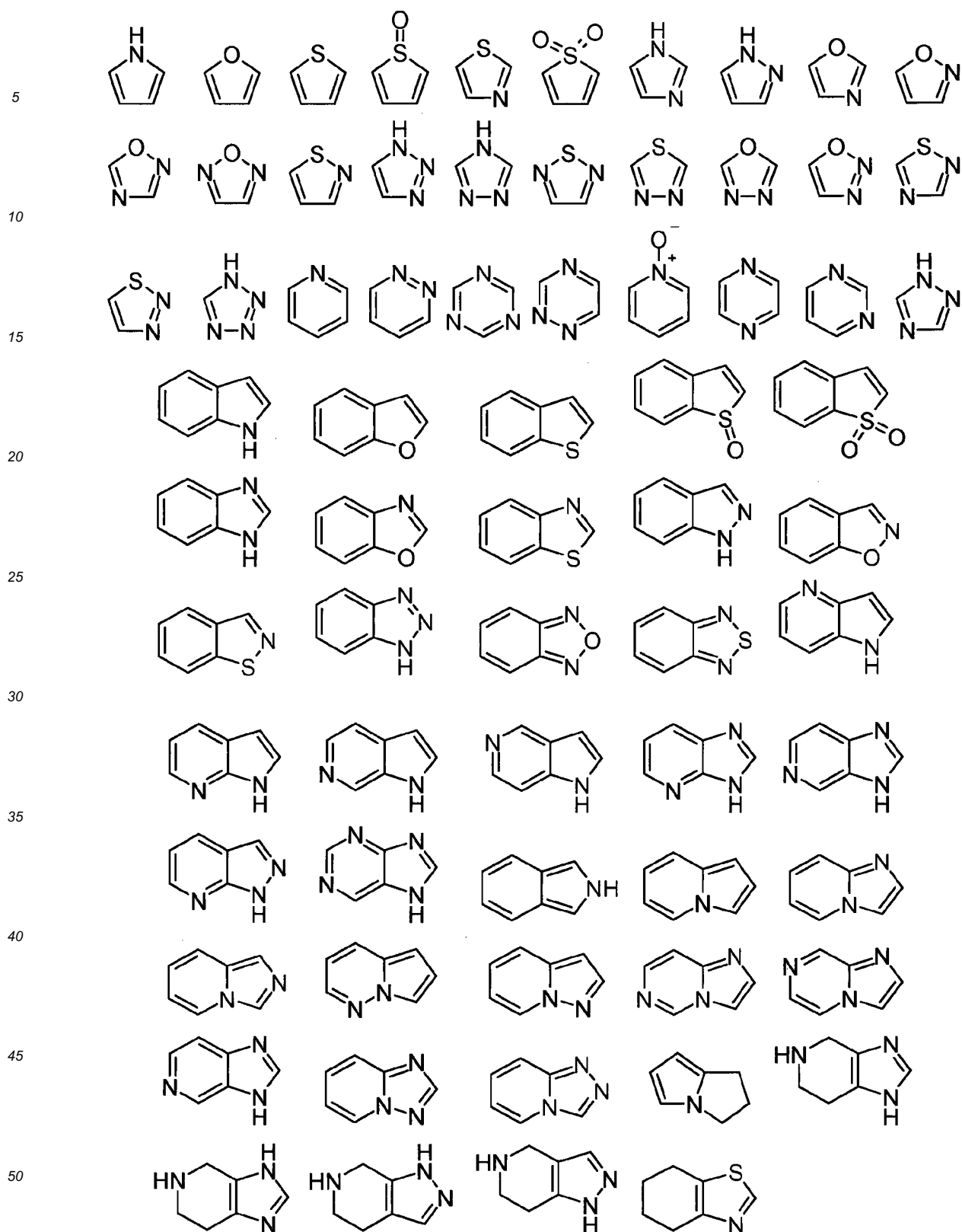
etc.

[0125] The above definition of **heterocyclylene** also applies if **heterocyclylene** is part of another group as in HO-**heterocyclyleneamino** or H<sub>2</sub>N-**heterocyclyleneoxy** for example.

[0126] **Heteroaryl** denotes monocyclic heteroaromatic rings or polycyclic rings with at least one heteroaromatic ring, which compared with the corresponding **aryl** or **cycloalkyl (cycloalkenyl)** contain, instead of one or more carbon atoms, one or more identical or different heteroatoms, selected independently of one another from among nitrogen, sulphur and oxygen, wherein the resulting group must be chemically stable. The prerequisite for the presence of **heteroaryl** is a heteroatom and a heteroaromatic system. If a **heteroaryl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. **Heteroaryl** itself may be linked as a substituent to the molecule via every suitable position of the ring system, both carbon and nitrogen.

[0127] Examples of **heteroaryl** are furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyridyl-*N*-oxide, pyrrolyl-*N*-oxide, pyrimidinyl-*N*-oxide, pyridazinyl-*N*-oxide, pyrazinyl-*N*-oxide, imidazolyl-*N*-oxide, isoxazolyl-*N*-oxide, oxazolyl-*N*-oxide, thiazolyl-*N*-oxide, oxadiazolyl-*N*-oxide, thiadiazolyl-*N*-oxide, triazolyl-*N*-oxide, tetrazolyl-*N*-oxide, indolyl, isoindolyl, benzofuryl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, indazolyl, isoquinolyl, quinolyl, quinoxalyl, cinnolyl, phthalazinyl, quinazolinyl, benzotriazinyl, indolizynyl, oxazolopyridyl, imidazopyridyl, naphthyridinyl, benzoxazolyl, pyridopyridyl, purinyl, pteridinyl, benzothiazolyl, imidazopyridyl, imidazothiazolyl, quinolyl-*N*-oxide, indolyl-*N*-oxide, isoquinolyl-*N*-oxide, quinazolinyl-*N*-oxide, quinoxalyl-*N*-oxide, phthalazinyl-*N*-oxide, indolizynyl-*N*-oxide, indazolyl-*N*-oxide, benzothiazolyl-*N*-oxide, benzimidazolyl-*N*-oxide etc.

[0128] Further examples are the structures illustrated below, which may be attached via each hydrogen-carrying atom (exchanged for hydrogen):

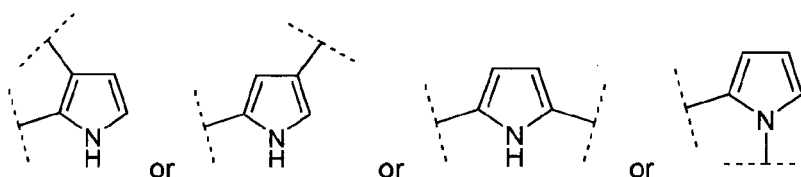


[0129] The above definition of **heteroaryl** also applies when **heteroaryl** is part of another group as in **heteroarylamino** or **heteroaryloxy**, for example.

[0130] If the free valency of a **heteroaryl** is saturated, a **heteroaromatic group** is obtained.

[0131] The term **heteroarylene** can therefore be derived from the previously defined **heteroaryl**. **Heteroarylene**, unlike **heteroaryl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing

a hydrogen atom from a **heteroaryl**. Corresponding groups are for example pyrrolyl and



etc.

**[0132]** The above definition of **heteroarylene** also applies when **heteroarylene** is part of another group as in HO-**heteroaryleneamino** or H<sub>2</sub>N-**heteroaryleneoxy**, for example.

**[0133]** The above-mentioned bivalent groups (alkylene, alkenylene, alkynylene etc.) may also be a part of composite groups (e.g. H<sub>2</sub>N-C<sub>1-4</sub>alkylene or HO-C<sub>1-4</sub>alkylene-). In this case one of the valencies is saturated by the attached group (in this case: -NH<sub>2</sub>, -OH), so that a composite group of this kind in this nomenclature amounts in total to only a monovalent substituent.

**[0134]** By **substituted** is meant that a hydrogen atom which is bound directly to the atom under consideration, is replaced by another atom or another group of atoms (**substituent**). Depending on the starting conditions (number of hydrogen atoms) mono- or polysubstitution may take place on one atom. Substitution with a particular substituent is only possible if the permitted valencies of the substituent and of the atom that is to be substituted correspond to one another and the substitution leads to a stable compound (*i.e.* to a compound which is not converted spontaneously, *e.g.* by rearrangement, cyclisation or elimination).

**[0135]** Bivalent substituents such as =S, =NR, =NOR, =NNRR, =NN(R)C(O)NRR, =N<sub>2</sub> or the like, may only be substituents at carbon atoms, wherein the bivalent substituent =O may also be a substituent at sulphur. Generally, substitution may be carried out by a bivalent substituent only at ring systems and requires replacement by two geminal hydrogen atoms, *i.e.* hydrogen atoms that are bound to the same carbon atom that is saturated prior to the substitution. Substitution by a bivalent substituent is therefore only possible at the group -CH<sub>2</sub>- or sulphur atoms of a ring system.

**[0136] Stereochemistry/Solvates/Hydrates:** Unless stated otherwise a structural formula given in the description or in the claims or a chemical name refers to the corresponding compound itself, but also encompasses the tautomers, stereoisomers, optical and geometric isomers (*e.g.* enantiomers, diastereomers, *E/Z* isomers, etc.), racemates, mixtures of separate enantiomers in any desired combinations, mixtures of diastereomers, mixtures of the forms mentioned hereinbefore (if such forms exist) as well as salts, particularly pharmaceutically acceptable salts thereof. The compounds and salts according to the invention may be present in solvated form (*e.g.* with pharmaceutically acceptable solvents such as *e.g.* water, ethanol etc.) or in unsolvated form. Generally, for the purposes of the present invention the solvated forms, *e.g.* hydrates, are to be regarded as of equal value to the unsolvated forms.

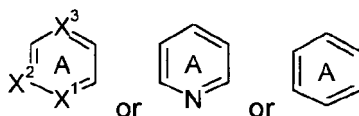
**[0137] Salts:** The term "**pharmaceutically acceptable**" is used herein to denote compounds, materials, compositions and/or formulations which are suitable, according to generally recognised medical opinion, for use in conjunction with human and/or animal tissue and do not have or give rise to any excessive toxicity, irritation or immune response or lead to other problems or complications, *i.e.* correspond overall to an acceptable risk/benefit ratio.

**[0138]** The term "**pharmaceutically acceptable salts**" relates to derivatives of the chemical compounds disclosed in which the parent compound is modified by the addition of acid or base. Examples of pharmaceutically acceptable salts include (without being restricted thereto) salts of mineral or organic acids in relation to basic functional groups such as for example amines, alkali metal or organic salts of acid functional groups such as for example carboxylic acids, etc. These salts include in particular acetate, ascorbate, benzenesulphonate, benzoate, besylate, bicarbonate, bitartrate, bromide/hydrobromide, Ca-edetate/edetate, camsylate, carbonate, chloride/hydrochloride, citrate, edisylate, ethane di-sulphonate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycolylarsnilate, hexylresorcinate, hydrabamine, hydroxymaleate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, malate, maleate, mandelate, methanesulphonate, mesylate, methylbromide, methylnitrate, methylsulphate, mucate, napsylate, nitrate, oxalate, pamoate, pantothenate, phenyl acetate, phosphate/diphosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulphamide, sulphate, tannate, tartrate, teoclate, toluenesulphonate, triethiodide, ammonium, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumin and procaine. Other pharmaceutically acceptable salts may be formed with cations of metals such as aluminium, calcium, lithium, magnesium, potassium, sodium, zinc, etc. (cf. also Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

**[0139]** The pharmaceutically acceptable salts of the present invention may be prepared starting from the parent compound which carries a basic or acidic functionality, by conventional chemical methods. Generally, such salts may be synthesised by reacting the free acid or base form of these compounds with a sufficient amount of the corresponding base or acid in water or an organic solvent such as for example ether, ethyl acetate, ethanol, isopropanol, acetonitrile (or mixtures thereof).

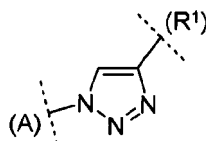
**[0140]** Salts of acids other than those mentioned above, which are useful for example for purifying or isolating the compounds from the reaction mixtures (e.g. trifluoroacetates), are also to be regarded as part of the invention.

**[0141]** In a representation such as for example



the letter A has the function of a ring designation in order to make it easier, for example, to indicate the attachment of the ring in question to other rings.

**[0142]** For bivalent groups in which it is crucial to determine which adjacent groups they bind and with which valency, the corresponding binding partners are indicated in brackets, where necessary for clarification purposes, as in the following representations:



or  $(R^2)-C(O)NH-$  or  $(R^2)-NHC(O)-$ ;

**[0143]** Groups or substituents are frequently selected from among a number of alternative groups/ substituents with a corresponding group designation (e.g.  $R^a$ ,  $R^b$  etc). If such a group is used repeatedly to define a compound according to the invention in different molecular parts, it must always be borne in mind that the various uses are to be regarded as totally independent of one another.

**[0144]** By a **therapeutically effective amount** for the purposes of this invention is meant a quantity of substance that is capable of obviating symptoms of illness or of preventing or alleviating these symptoms, or which prolong the survival of a treated patient.

#### List of abbreviations

**[0145]**

aa	amino acid
Ac	acetyl
equiv.	equivalent(s)
Ar	(hetero)aryl
ATP	adenosine triphosphate
Boc	<i>tert</i> -butoxycarbonyl
BSA	bovine serum albumin
Bu	butyl
d	day(s)
TLC	thin layer chromatography
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEA	diethylamine
DIC	diisopropylcarbodiimide
DIPEA	<i>N</i> -ethyl- <i>N,N</i> -diisopropylamine (HÜNIG-base)
DMA	<i>N,N</i> -dimethylacetamide

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(continued)

	DMAP	4-dimethylaminopyridine
5	DMF	<i>N,N</i> -dimethylformamide
	DMF-DMA	<i>N,N</i> -dimethylformamide-dimethylacetal
	DMSO	dimethylsulphoxide
	dppf	1,1'-bis(diphenylphosphino)ferrocene
10	EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> 4-ethylcarbodiimide hydrochloride
	ESI	electron spray ionization
	Et	ethyl
15	EtOH	ethanol
	h	hour(s)
	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyl-uronium hexafluorophosphate
	HCl	hydrochloric acid
20	het	hetero
	HPLC	high performance liquid chromatography
	HÜNIG base	<i>N</i> -ethyl- <i>N,N</i> -diisopropylamine
25	<i>i</i>	iso
	<i>i</i> Pr <sub>2</sub> NEt	diisopropylethylamine (HÜNIG base)
	<i>i</i> PrOH	isopropanol
	cat.	catalyst, catalytic
30	conc.	concentrated
	LC	liquid chromatography
	sln.	solution
35	M	molar
	Me	methyl
	MeOH	methanol
	min	minute(s)
40	mL	millilitres
	MPLC	medium pressure liquid chromatography
	MS	mass spectrometry
45	MW	microwave
	N	normal
	NMP	<i>N</i> -methylpyrrolidinone
	PBS	phosphate-buffered saline
50	Pd-dppf	1,1'-bis(diphenylphosphino)ferrocene palladium(II)-dichloride dichloromethane
	Ph	phenyl
	PK	pharmacokinetics
55	Pr	propyl
	R <sub>f</sub> (Rf)	retention factor
	RP	reversed phase

(continued)

RT	ambient temperature
s	second(s)
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate
TEA	triethylamine
<i>tert</i>	tertiary
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tos	tosyl
<i>t</i> <sub>Ret</sub>	retention time (HPLC)
TRIS	tris(hydroxymethyl)-aminomethane
UV	ultraviolet

**[0146]** Features and advantages of the present invention will become apparent from the following detailed Examples, which illustrate the fundamentals of the invention by way of example, without restricting its scope:

#### Preparation of the compounds according to the invention

##### General

**[0147]** Unless stated otherwise, all the reactions are carried out in commercially obtainable apparatus using methods that are commonly used in chemical laboratories. Starting materials that are sensitive to air and/or moisture are stored under protective gas and corresponding reactions and manipulations therewith are carried out under protective gas (nitrogen or argon).

**[0148]** The compounds are named according to the Beilstein rules using the Autonom software (Beilstein). If a compound is to be represented both by a structural formula and by its nomenclature, in the event of a conflict the structural formula is decisive.

**[0149]** **Microwave reactions** are carried out in an initiator/reactor made by Biotage or Synthos 3000 and Monowave 300 made by the company Anton Paar in sealed containers (preferably 2, 5 or 20 mL), preferably with stirring.

##### Chromatography

**[0150]** Thin layer chromatography is carried out on ready-made TLC plates of silica gel 60 on glass (with fluorescence indicator F-254) made by Merck.

**[0151]** The **preparative high pressure chromatography (HPLC)** of the example compounds according to the invention is carried out with columns made by Waters (names: Sunfire C18, 5  $\mu$ m, 30 x 100 mm Part. No. 186002572; X-Bridge C18, 5  $\mu$ m, 30 x 100 mm Part. No. 186002982).

**[0152]** The compounds are eluted using either different gradients of H<sub>2</sub>O/acetonitrile or H<sub>2</sub>O/MeOH, wherein preferably 0.1 % HCOOH is added to the water (acid conditions). For chromatography under basic conditions H<sub>2</sub>O/acetonitrile gradients are also used, and the water is made basic according to the following recipe: 5 mL of an ammonium hydrogen carbonate solution (158 g to 1 L H<sub>2</sub>O) and 2 mL ammonia (7M in MeOH) are made up to 1 L with H<sub>2</sub>O.

**[0153]** The **normal-phase preparative high pressure chromatography (HPLC)** of the example compounds according to the invention is carried out with columns made by Macherey & Nagel (name: Nucleosil, 50-7, 40 x 250 mm) and VDSoptilab (name: Kromasil 100 NH<sub>2</sub>, 10  $\mu$ M, 50 x 250 mm). The compounds are eluted using different gradients of DCM/ MeOH, with 0.1 % NH<sub>3</sub> added to the MeOH.

**[0154]** The **analytical HPLC (reaction monitoring)** of intermediate compounds is carried out with columns made by Agilent, Waters and Phenomenex. The analytical equipment is also provided with a mass detector in each case.



**HPLC mass spectroscopy/UV spectrometry**

**[0155]** The retention times/MS-ESI<sup>+</sup> for characterising the example compounds according to the invention are produced using an HPLC-MS apparatus (high performance liquid chromatography with mass detector) made by Agilent. Compounds that elute at the injection peak are given the retention time  $t_{\text{Ret}} = 0.00$ .

**HPLC-methods**Preparative**prep. HPLC1****[0156]**

HPLC: 333 and 334 Pumps  
 Column: Waters X-Bridge C18, 5  $\mu\text{m}$ , 30 x 100 mm, Part. No. 186002982  
 Eluant: A: 10 mM  $\text{NH}_4\text{HCO}_3$  in  $\text{H}_2\text{O}$ ; B: acetonitrile (HPLC grade)  
 Detection: UV/Vis-155  
 Flow: 50 mL/min  
 Gradient: 0.00 min: 5 % B  
 3.00 - 15.00 min: variable (see individual methods)  
 15.00 - 17.00 min: 100 % B

**prep. HPLC2****[0157]**

HPLC: 333 and 334 Pumps  
 Column: Waters Sunfire C18, 5  $\mu\text{m}$ , 30 x 100 mm, Part. No. 186002572  
 Eluant: A:  $\text{H}_2\text{O}$  + 0.2 %  $\text{HCOOH}$ ; B: acetonitrile (HPLC grade) + 0.2 %  $\text{HCOOH}$   
 Detection: UV/Vis-155  
 Flow: 50 mL/min  
 Gradient: 0.00 min: 5 % B  
 3.00 - 15.00 min: variable (see individual methods)  
 15.00 - 17.00 min: 100 % B

Analytical**Method A****[0158]**

**HPLC** Agilent 1100 Series  
**MS** 1100 Series LC/MSD SL (MM-ES + APCI, + 3000 V, Quadrupol, G1956B)  
**MSD signal settings** Scan pos 120 - 750  
**column** Waters, XBridge, C18, 3.5  $\mu\text{m}$ , 135 Å, 30 x 2.1 mm column, Part. No: 186003020  
**eluant** **A:** 5 mM  $\text{NH}_4\text{HCO}_3$ /20 mM  $\text{NH}_3$  (pH = 9.5)  
**B:** acetonitrile (HPLC grade)  
**detection signal** UV 254/214 nm (bandwidth 8, reference off)  
**spectrum** range: 190 - 400 nm; step: 2.0 nm  
**peak width** > 00025 min (0.05 s)  
**injection** 2  $\mu\text{L}$  standard injection

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(continued)

	<b>flow</b>	1.0 mL/min	
	<b>column temperature</b>	35 °C	
5	<b>gradient</b>	0.0 - 1.0 min	15 % → 95 % B
		1.0 - 1.6min	95 % B
		1.6 - 1.7min	95 % → 15 % B
		1.7 - 2.3min	15 % B

10

### Method B

[0159]

15	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	1100 Series LC/MSD SL (MM-ES + APCI, + 3000 V, Quadrupol, G 1956B)	
	<b>MSD signal settings</b>	Scan pos 120 - 750	
	<b>column</b>	Waters, XBridge, C18, 3.5 µm, 135 Å, 30 x 2.1 mm column, Part. No.: 186003020	
20	<b>eluant</b>	<b>A:</b> 5 mM NH <sub>4</sub> HCO <sub>3</sub> /20 mM NH <sub>3</sub> (pH = 9.5) <b>B:</b> MeOH (HPLC grade)	
	<b>detection signal</b>	UV 254/214 nm (bandwidth 8, reference off)	
	<b>spectrum</b>	range: 190 - 400 nm; step: 2.0 nm	
25	<b>peak width</b>	> 00025 min (0.05 s)	
	<b>injection</b>	2 µL standard injection	
	<b>flow</b>	1.0 mL/min	
	<b>column temperature</b>	40 °C	
	<b>gradient</b>	0.0 - 1.0 min	20 % → 95 % B
30		1.0 - 2.0 min	95 % B
		2.0 - 2.1 min	95 % → 20 % B
		2.1 - 2.3 min	20 % B

35

### Method C

[0160]

40	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	1200 Series LC/MSD (API-ES + 3000 V, Quadrupol, G6140A)	
	<b>MSD signal settings</b>	Scan pos 150 - 750	
	<b>column</b>	Agilent. Zorbax SB, C8, 3.5 µm, 80 Å, 50x2.1 mm column, Part. No.: 871700-906	
	<b>eluant</b>	<b>A:</b> water + 0.11 % formic acid <b>B:</b> acetonitrile (HPLC grade) + 0.1 % formic acid	
45	<b>detection signal</b>	UV 254/214/230 nm (bandwidth 8, reference off)	
	<b>spectrum</b>	range: 190 - 450 nm; step: 4.0 nm	
	<b>peak width</b>	> 0.01 min (0.2 s)	
	<b>injection</b>	1.5 µL standard injection	
50	<b>flow</b>	1.1 mL/min	
	<b>column temperature</b>	45 °C	
	<b>gradient</b>	0.0 - 1.75 min	15 % → 95 % B
		1.75 - 1.9 min	95 % B
		1.9 - 1.92 min	95 % → 15 % B
55		1.92 - 2.1 min	15 % B

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### Method D

[0161]

5	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	1100 Series LC/MSD SL (MM-ES + APCI, + 2500 V, Quadrupol, G1956B)	
	<b>MSD signal settings</b>	Scan pos 70 - 500	
	<b>column</b>	Agilent Zorbax SB, C8, 3.5 µm, 80 Å, 50 x 2.1 mm column, Part. No.: 871700-906	
10	<b>eluant</b>	<b>A:</b> water + 0.11 % formic acid <b>B:</b> MeOH (HPLC grade)	
	<b>detection signal</b>	UV 254/214/230 nm (bandwidth 8, reference off)	
	<b>spectrum</b>	range: 190 - 450 nm; step: 4.0 nm	
15	<b>peak width</b>	> 0.01 min (0.2 s)	
	<b>injection</b>	1.5 µL standard injection	
	<b>flow</b>	1.0 mL/min	
	<b>column temperature</b>	45 °C	
20	<b>gradient</b>	0.0 - 1.5 min	20 % → 95 % B
		1.5 - 2.1 min	95 % B
		2.1 - 2.2min	95 % → 20 % B
		2.2 - 2.4min	20 % B

### Method E

[0162]

30	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	1100 Series LC/MSD SL (MM-ES + APCI, + 3000 V, Quadrupol, G1956B)	
	<b>MSD signal settings</b>	Scan pos 100 - 750	
	<b>column</b>	Waters, XBridge, C18, 3.5 µm, 135 Å, 30x2.1 mm column, Part. No.: 186003020	
35	<b>eluant</b>	<b>A:</b> 5 mM NH <sub>4</sub> HCO <sub>3</sub> /20 mM NH <sub>3</sub> (pH = 9.5) <b>B:</b> acetonitrile (HPLC grade)	
	<b>detection signal</b>	UV 254/214 nm (bandwidth 8, reference off)	
	<b>spectrum</b>	range: 190 - 400 nm; step: 2.0 nm	
	<b>peak width</b>	> 0005 min (0.1 s)	
40	<b>injection</b>	2 µL standard injection	
	<b>flow</b>	1.0 mL/min	
	<b>column temperature</b>	35°C	
45	<b>gradient</b>	0.0 - 1.0 min	15 % → 95 % B
		1.0 - 1.6min	95 % B
		1.6 - 1.7 min	95 % → 15 % B
		1.7 - 2.3 min	15 % B

### Method F

[0163]

55	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	1200 Series LC/MSD (API-ES + 2500 V, Quadrupol, G6140A)	
	<b>MSD signal settings</b>	Scan pos 75 - 500	
	<b>column</b>	Agilent Zorbax SB, C8, 3.5 µm, 80 Å, 50 x 2.1 mm column, Part. No.: 871700-906	
	<b>eluant</b>	<b>A:</b> water + 0.11 % formic acid	

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(continued)

		<b>B:</b> acetonitrile (HPLC grade) + 0.1 % formic acid	
	<b>detection signal</b>	UV 254/214/230 nm (bandwidth 8, reference off)	
5	<b>spectrum</b>	range: 190 - 450 nm; step: 4.0 nm	
	<b>peak width</b>	> 0.01 min (0.2 s)	
	<b>injection</b>	1.5 µL standard injection	
	<b>flow</b>	1.1 mL/min	
	<b>column temperature</b>	45 °C	
10	<b>gradient</b>	0.0 - 1.75 min	15 % → 95 % B
		1.75 - 1.9min	95 % B
		1.9 - 1.92 min	95 % → 15 % B
		1.92 - 2.1min	15 % B

### Method G

[0164]

20	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	1100 Series LC/MSD (API-ES +/- 3000 V, Quadrupol, G1946D)	
	<b>MSD signal settings</b>	Scan pos 120 - 900, Scan neg 120 - 900	
	<b>column</b>	phenomenex; Part. No. 00M-4439-BO-CE; Gemini 3 µm, C18, 110 Å; 20 x 2.0 mm column	
25	<b>eluant</b>	A: 5 mM NH <sub>4</sub> HCO <sub>3</sub> /20 mM NH <sub>3</sub> (pH = 9.5)	
		B: acetonitrile (HPLC grade)	
	<b>detection signal</b>	UV 254 nm (bandwidth 1, reference off)	
	<b>spectrum</b>	range: 250 - 400 nm; step: 1 nm	
	<b>peak width</b>	< 0.01 min (0.1 s)	
30	<b>injection</b>	10 µL standard injection	
	<b>flow</b>	1.0 mL/min	
	<b>column temperature</b>	40 °C	
	<b>gradient</b>	0.0 - 2.5 min	5 % → 95 % B
		2.5 - 2.8min	95 % B
35		2.8 - 3.1min	95 % → 5 % B

### Method H

[0165]

40	<b>HPLC</b>	Agilent G1312A binary pump with Waters 2996 PDA detector	
	<b>MS</b>	Waters ZQ	
	<b>MSD Signal Settings</b>	Scan pos 150 - 850	
45	<b>column</b>	Waters; Part. No. 186001295; Atlantis dC18, 2.1 x 100.0 mm, 3 µm column	
	<b>eluant</b>	<b>A:</b> 0.1 % formic acid in water	
		<b>B:</b> 0.1 % formic acid in acetonitrile (HPLC grade)	
	<b>detection signal</b>	UV 215 nm	
50	<b>spectrum</b>	range: 200 - 420 nm; step: 1 nm	
	<b>injection</b>	3 µL	
	<b>flow</b>	0.6 mL/min	
	<b>column temperature</b>	40 °C	
	<b>gradient</b>	0.0 min	5 % B
55		0.0 - 5.0 min	5 % → 100 % B
		5.0 - 5.4 min	100 % B
		5.4 - 5.42 min	100 % → 5 % B

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(continued)

5.42 - 7.0 min

5 % B

### 5 Method I

[0166]

10	<b>HPLC</b>	Shimadzu Prominence Series
	<b>MS</b>	Shimadzu LCMS-2010EV system
	<b>MSD Signal Settings</b>	Scan pos 100 - 1000
	<b>column</b>	Waters; Part. No. 186001291; Atlantis dC18, 2.1 x 50.0 mm, 3 µm column
	<b>eluant</b>	<b>A:</b> 0.1 % formic acid in water
15		<b>B:</b> 0.1 % formic acid in acetonitrile (HPLC grade)
	<b>detection signal</b>	UV 215 nm
	<b>spectrum</b>	range: 210 - 420 nm; step: 1 nm
	<b>injection</b>	3 µL
	<b>flow</b>	1.0 mL/min
20	<b>column temperature</b>	40 °C
	<b>gradient</b>	0.0 min 5 % B
		0.0 - 2.5 min 5 % → 100 % B
		2.5 - 2.7 min 100 % B
		2.7 - 2.71 min 100 % → 5 % B
25		2.71 - 3.50 min 5 % B

### Method J

30 [0167]

	<b>HPLC</b>	Agilent G1312A binary pump with Waters 2996 PDA detector
	<b>MS</b>	Waters LCT (MS5) or Waters ZQ (MS10)
	<b>MSD Signal Settings</b>	Scan pos 150 - 850
35	<b>column</b>	Phenomenex; Part No. 00D-4453-B0; Gemini C18, 2.0 x 100.0 mm, 3 µm column
	<b>eluant</b>	<b>A:</b> 2 mM NH <sub>4</sub> HCO <sub>3</sub> buffered to pH = 10
		<b>B:</b> acetonitrile (HPLC grade)
	<b>detection signal</b>	UV 215 nm
40	<b>spectrum</b>	range: 200 - 420 nm; step: 1 nm
	<b>injection</b>	3 µL
	<b>flow</b>	0.5 mL/min
	<b>column temperature</b>	50 °C
	<b>gradient</b>	0.0 min 5 % B
45		0.0 - 5.5 min 5 % → 100 % B
		5.5 - 5.9min 100 % B
		5.9 - 5.92min 100 % → 5 % B
	5.92 - 9.0 min	5 % B

50

### Method K

[0168]

55	<b>HPLC</b>	Shimadzu Prominence Series
	<b>MS</b>	Shimadzu LCMS-2010EV System
	<b>MSD Signal Settings</b>	Scan pos 100 - 1000

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(continued)

	<b>column</b>	Waters; Part. No. 186001287; Atlantis dC18, 2.1 x 30.0 mm, 3 µm column	
	<b>eluant</b>	<b>A:</b> 0.1 % formic acid in water	
5		<b>B:</b> 0.1 % formic acid in acetonitrile (HPLC grade)	
	<b>detection signal</b>	UV 215 nm	
	<b>spectrum</b>	range: 220 - 420 nm; step: 1 nm	
	<b>injection</b>	3 µL	
	<b>flow</b>	1.0 mL/min	
10	<b>column temperature</b>	40 °C	
	<b>gradient</b>	0.0 min	5 % B
		0.0 - 1.5min	5 % → 100 % B
		1.5 - 1.6min	100 % B
15		1.6 - 1.61 min	100 % → 5 % B

### Method L

#### [0169]

20	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	1100Series LC/MSD SL (MM-ES + APCI, + 3000 V, Quadrupol, G 1956B)	
	<b>MSD Signal Settings</b>	Scan pos 120 - 750	
	<b>column</b>	Waters, XBridge, C18, 5.0 µm, 50 x 2.1 mm column, Part. No.: 186003108	
25	<b>eluant</b>	<b>A:</b> 5 mM NH <sub>4</sub> HCO <sub>3</sub> / 20 mM NH <sub>3</sub> (pH = 9.5)	
		<b>B:</b> acetonitrile (HPLC grade)	
	<b>detection signal</b>	UV 254/214 nm (bandwidth 8, reference off)	
	<b>spectrum</b>	range: 190 - 400 nm; step: 2.0 nm	
30	<b>peak width</b>	> 00025 min (0.05 s)	
	<b>injection</b>	2 µL standard injection	
	<b>flow</b>	1.2 mL/min	
	<b>column temperature</b>	35 °C	
35	<b>gradient</b>	0.0 - 1.25min	5 % → 100 % B
		1.25 - 2.0 min	100 % B
		2.0 - 3.1 min	100 % → 5 % B

### Method M

#### [0170]

	<b>HPLC</b>	Agilent 1100 Series	
	<b>MS</b>	Agilent LC/MSD SL	
45	<b>MSD Signal Settings</b>	MS: Positive and negative Mass range: 120 - 900 m/z	
	<b>column</b>	Waters, Xbridge C18™, 2.5µm, 2.1 x20 mm, Part.No. 186003201	
	<b>eluant</b>	<b>A:</b> 20 mM NH <sub>4</sub> HCO <sub>3</sub> /NH <sub>3</sub> pH 9	
		<b>B:</b> acetonitrile (HPLC grade)	
50	<b>detection signal</b>	UV, bandwidth 170 nm, reference off	
	<b>spectrum</b>	range: 230 - 400 nm; step: 1.0 nm	
	<b>peak width</b>	< 0.01 min	
	<b>injection</b>	5 µL standard injection	
	<b>flow</b>	1.0 mL/min	
55	<b>column temperature</b>	60 °C	
	<b>gradient</b>	0.0 min	10 % B
		0.0 - 1.5 min	10 % → 95 % B

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(continued)

1.5 - 2.0 min	95 % B
2.0 - 2.1 min	95 % → 10 % B

5

### Method N

[0171]

10	<b>HPLC</b>	Agilent 1100 Series
	<b>MS</b>	1200 Series LC/MSD (API-ES +/- 3000 V, Quadrupol, G6130A)
	<b>MSD Signal Settings</b>	Scan pos 105-1200, Scan neg. 105-1200
	<b>column</b>	Waters, XBridge, C18, 5 µm, 135 Å, 30 x 2.1 mm column, Part. No.: 186003108
15	<b>eluant</b>	<b>A:</b> 5 mM NH <sub>4</sub> HCO <sub>3</sub> /19 mM NH <sub>3</sub> (pH = 9.5) <b>B:</b> acetonitrile (HPLC grade)
	<b>detection signal</b>	UV 254/230 nm (bandwidth 8, reference off)
	<b>spectrum</b>	range: 190 - 450 nm; step: 4.0 nm
20	<b>peak width</b>	> 0.03 min (0.5 s)
	<b>injection</b>	2 µL standard injection
	<b>flow</b>	1.2 mL/min
	<b>column temperature</b>	35 °C
25	<b>gradient</b>	0.0 - 1.25 min                      5 % → 95 % B 1.25 - 2.0 min                      95 % B 2.0 - 2.01 min                      95 % → 5 % B 2.01 - 3.0 min                      5 % B

30 Method O

[0172]

35	<b>HPLC</b>	Agilent 1200 Series
	<b>MS</b>	1100 Series LC/MSD (API-ES +/- 3000 V, Quadrupol, G1946D)
	<b>MSD Signal Settings</b>	Scan pos 105-1200, Scan neg. 105-1200
	<b>column</b>	Waters, XBridge, C18, 5 µm, 135 Å, 30x2.1 mm column, Part. No.: 186003108
	<b>eluant</b>	<b>A:</b> 5 mM NH <sub>4</sub> HCO <sub>3</sub> /19 mM NH <sub>3</sub> (pH = 9.5) <b>B:</b> acetonitrile (HPLC grade)
40	<b>detection signal</b>	UV 254/230 nm (bandwidth 8, reference off)
	<b>spectrum</b>	range: 190 - 450 nm; step: 4.0 nm
	<b>peak width</b>	> 0.03 min (0.5 s)
	<b>injection</b>	2 µL standard injection
45	<b>flow</b>	1.2 mL/min
	<b>column temperature</b>	35 °C
	<b>gradient</b>	0.0 - 1.25 min                      5 % → 100 % B 1.25 - 2.0 min                      100 % B 2.0 - 2.01 min                      100 % → 5 % B 2.01 - 3.0 min                      5 % B

50

### Method P

55 [0173]

<b>HPLC</b>	Agilent 1100 Series
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## EP 2 655 358 B1

(continued)

<b>MS</b>	Agilent LC/MSD SL
<b>MSD Signal Settings</b>	MS: Positive and negative
	Mass range: 120 - 800 m/z
<b>column</b>	Waters, XBridge™ C18, 2.5 μm, 2.1 x 20 mm; Part.No. 186003201
<b>eluant</b>	<b>A:</b> 0.1 % NH <sub>3</sub> (pH = 9-10)
	<b>B:</b> acetonitrile (HPLC grade)
<b>detection signal</b>	UV, bandwidth 170 nm, reference off
<b>spectrum</b>	range: 230 - 400 nm; step: 2.0 nm
<b>peak width</b>	< 0.01 min
<b>injection</b>	5 μL standard injection
<b>flow</b>	1.0 mL/min
<b>column temperature</b>	60 °C
<b>gradient</b>	0.0 min 5 % B
	0.0 - 2.5 min 5 % → 95 % B
	2.5 - 2.8 min 95 % B
	2.81 - 3.1 min 95 % → 5 % B

### Method Q

[0174]

<b>HPLC</b>	Agilent 1100
<b>column</b>	AD-H (Messrs. Chiralcel; 4.6 x 150 mm)
<b>eluant</b>	MeOH + 0.1 % DEA
<b>flow</b>	0.7 mL/min
<b>column temperature</b>	40 °C
<b>gradient</b>	isocratic

### Method R

[0175]

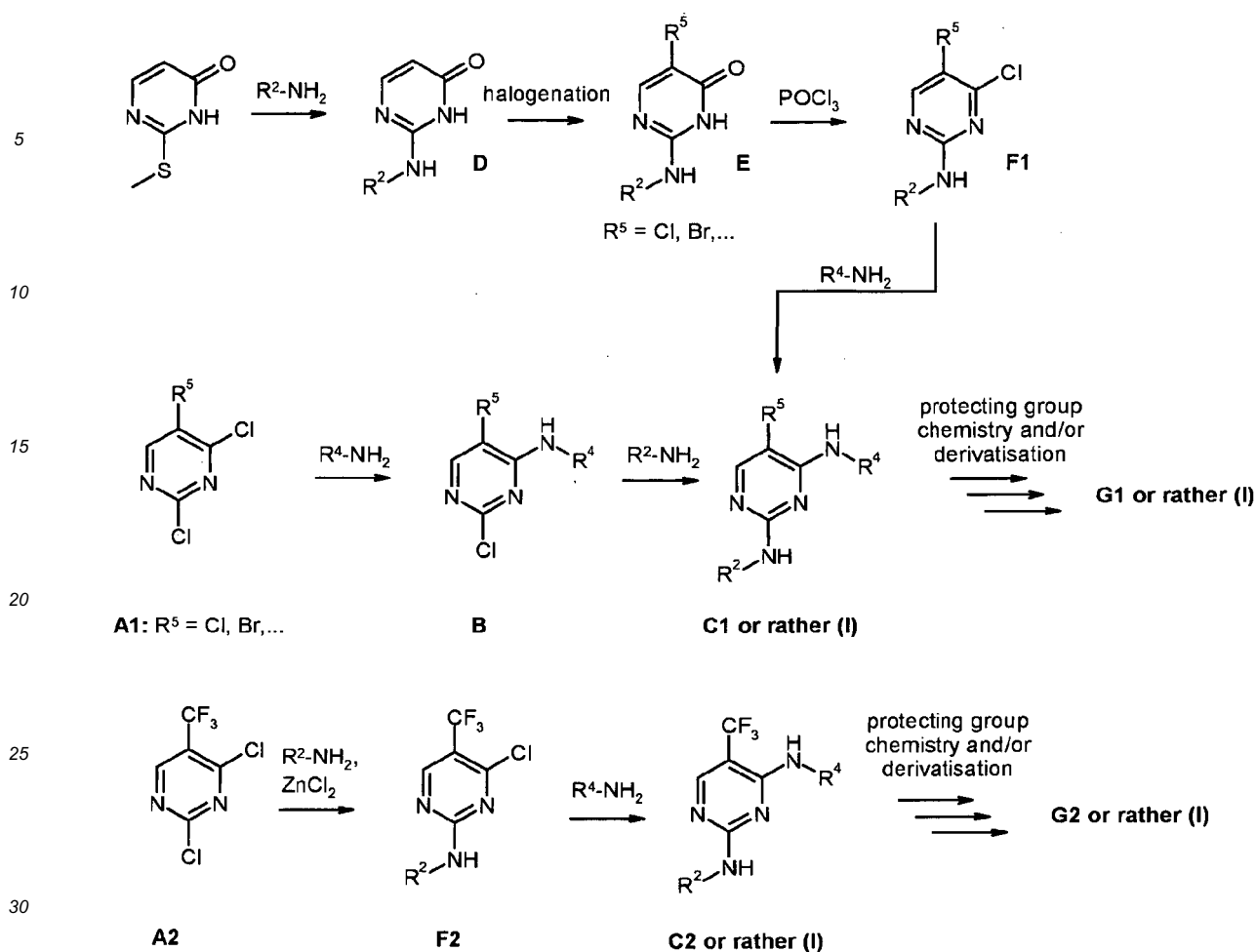
<b>HPLC</b>	Agilent 1100
<b>column</b>	LUX2 (Messrs. Phenomenex; 4.6 x 150 mm)
<b>eluant</b>	MeOH + 0.1 % DEA
<b>flow</b>	0.7 mL/min
<b>column temperature</b>	40 °C
<b>gradient</b>	isocratic

[0176] The compounds according to the invention are prepared by the methods of synthesis described hereinafter, in which the substituents of the general formulae have the meanings given hereinbefore. These methods are intended as an illustration of the invention, without restricting its subject matter and the scope of the compounds claimed to these examples. Where the preparation of starting compounds is not described, they are commercially obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in the literature are prepared according to the published methods of synthesis.

### General formula scheme and summary of the synthesis route

[0177]





[0178] In principle, 2,4-diaminopyrimidine derivatives may be prepared from correspondingly substituted chloropyrimidines. The reactivity of these chloropyrimidines is controlled by the substituent in position 5, with the result that different synthesis strategies have to be adopted depending on the nature of this substituent.

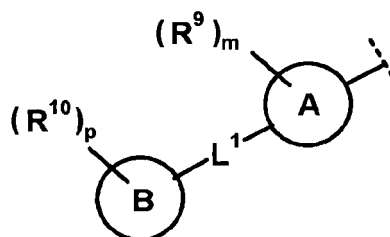
[0179] For all the substituents with the exception of the trifluoromethyl group ( $-\text{CF}_3$ ) functionalisation may be carried out in the 4 position as the first step. By reacting the 2,4-dichloro compound **A1** with the corresponding amine  $R^4\text{-NH}_2$  the intermediate **B** is obtained, which may in turn be converted into the 2,4-diaminopyrimidine **C1** by reaction with a (hetero)aromatic amine  $R^2\text{-NH}_2$ .

[0180] Alternatively, 2,4-diaminopyrimidines **C1** may also be prepared starting from 2-methylsulphonyl-3H-pyrimidin-4-one by reacting with a (hetero)aromatic amine  $R^2\text{-NH}_2$  followed by halogenation in position 5 via the intermediates **D** and **E**. The cyclic amide **E** may be reacted with phosphoryl chloride to obtain the 4-chloropyrimidine **F1**, which in turn leads to **C1** by reaction with a correspondingly configured amine  $R^4\text{-NH}_2$ .

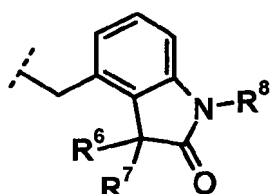
[0181] 2,4-Dichloropyrimidine **A2** substituted in position 5 by a trifluoromethyl group may be reacted in the presence of zinc chloride with a (hetero)aromatic amine  $R^2\text{-NH}_2$  and thus yields the 4-chloropyrimidine **F2**, which may in turn be reacted with amines  $R^4\text{-NH}_2$  and converted into the 2,4-diaminopyrimidine **C2**.

[0182] The 2,4-diaminopyrimidines **C1** and **C2** may on the one hand be end compounds (I) according to the invention or on the other hand may be prepared using correspondingly protected amines in positions 2 and 4, deprotected by conventional methods and then converted into the actual end compounds (I) designated **G1** or **G2** by one or more derivatisation steps such as e.g. amide formation, alkylation or amination reactions. Instead of protected amines it is also possible to use synthesis components which can be directly functionalised or derivatised without recourse to protective groups.

[0183] In end compounds (I) according to the invention the group  $R^2$  corresponds to a grouping having the structure

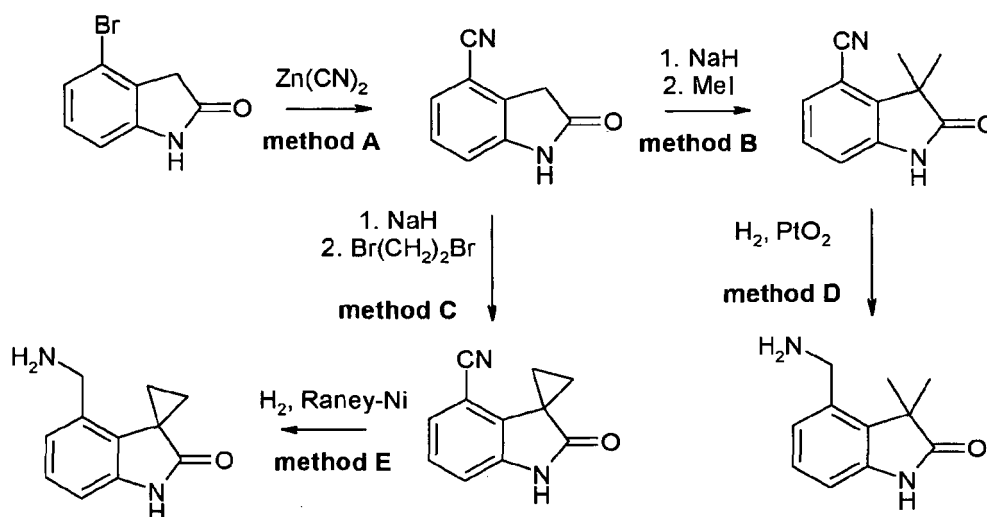


and the group  $R^4$  to a grouping having the structure



# 1. Preparation of the oxindole components (= amine $R^4-NH_2$ )

[0184]



**[0185] 1.1 Preparation of 4-cyanooxindole (method A).** 4-bromoxindole (2.0 g, 9.43 mmol), zinc cyanide (680 mg, 5.68 mmol), tris(bisbenzylideneacetone)dipalladium (250 mg, 0.27 mmol) and 1,1'-diphenylphosphineferrocene (300 mg, 0.54 mmol) are stirred in anhydrous DMF (10 mL) for 2 h at 140°C under argon. The reaction mixture is cooled and poured onto 30 % aqueous ethanol. The precipitate is filtered off, digested with water and EtOH and dried.

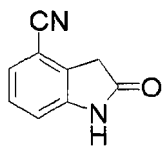
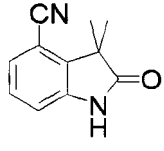
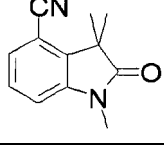
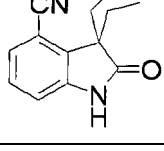
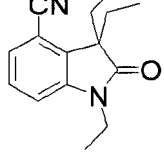
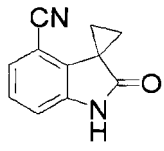
**[0186] 1.2 Preparation of 4-cyano-3,3-dimethyloxindole (method B).** 4-cyanooxindole (6.80 g, 43.0 mmol) in anhydrous THF (40 mL) is combined with sodium hydride (60 % dispersion in white oil, 7.0 g, 175 mmol) at - 72°C under argon and stirred for 20 min at this temperature. Methyl iodide (4.0 mL, 64.3 mmol) is added, the reaction mixture is slowly heated to RT and stirred for 48 h. The mixture is combined at - 72°C with saturated ammonium chloride solution (38 mL) and divided between water and EtOAc. The aqueous phase is exhaustively extracted with EtOAc, the combined organic phases are washed with water and saturated saline solution, dried on sodium sulphate, filtered and evaporated down. The crude product is crystallised or purified by column chromatography.

**[0187]** Additional alkylation at the nitrogen is obtained using 6 equiv. NaH and 7 equiv. methyl iodide. Moreover, an alkylating agent other than methyl iodide may be used.

**[0188] 1.3 Preparation of 4-cyano-3-spirocyclopropyloxindole (method C).** 4-cyanooxindole (500 mg, 3.16 mmol) are taken up in 2 mL anhydrous DMF and combined with 248  $\mu$ L (2.85 mmol) 1,2-dibromoethane. After the solution has been cooled to 0°C, 379 mg NaH (9.5 mmol, 60 % dispersion in oil) are added and the reaction mixture is stirred for 16 h at RT. It is mixed with several millilitres of saturated aqueous ammonium chloride solution, extracted 3  $\times$  with EtOAc

and the combined organic phases are dried on sodium sulphate. After elimination of the volatile constituents in vacuo the residue is purified by chromatography (RP phase).

Table 1

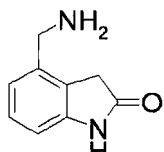
intermediate	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
	0.44	-	C
	0.72	187.2	C
	0.84	201.2	C
	0.75	215.2	C
	1.03	243.2	C
	1.15	189	L

**[0189] 1.4 Preparation of 4-aminomethyl-3,3-dimethyloxindole (method D).** 4-cyano-3,3-dimethyloxindole (3.70 g, 19.9 mmol) in MeOH (35 mL) and 6 N HCl (15 mL) is mixed with platinum oxide (500 mg) and hydrogenated for 17 h at RT under a hydrogen pressure of 5 bar. The reaction mixture is filtered and evaporated down.

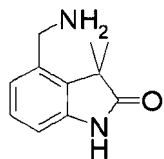
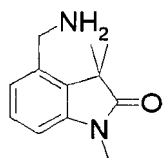
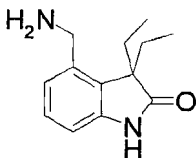
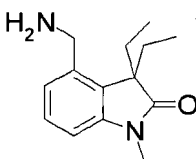
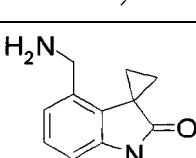
**[0190]** 4-cyano-3-spirocyclopropyloxindole is hydrogenated using Raney nickel and methanolic ammonia as solvent (method E).

**[0191]** Further 4-cyanooxindoles may also be hydrogenated analogously.

Table 2

intermediate	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
	0.13	163.2	C

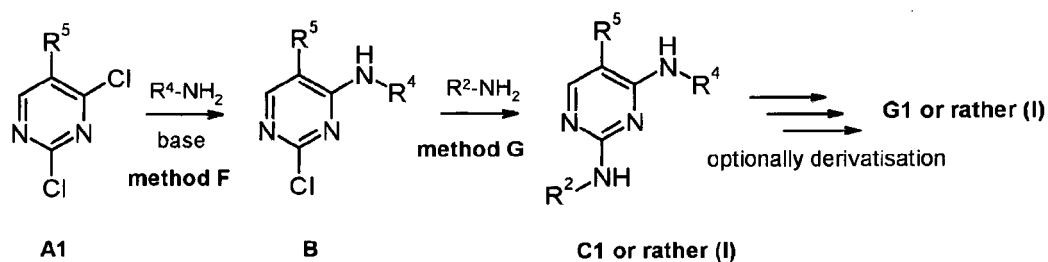
(continued)

intermediate	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
	0.13	191.0	C
	0.18	205.2	C
	0.16	219.2	C
	0.37	247.2	C
	1.07	185	G

## 2. Preparation of the intermediates/example compounds C1 and G1 or (I)

### 2.1 Variant 1

[0192]

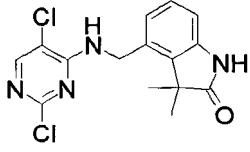
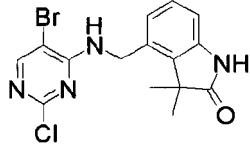
 $R^5 = \text{Cl, Br}$ 

#### 2.1.1 Synthesis of intermediate B-1 (method F).

[0193] 2,4,5-trichloropyrimidine **A1-1** (0.30 mL, 2.61 mmol) in anhydrous DCM is combined at 0°C with *N*-ethyldiisopropylamine (1.4 mL, 8.0 mmol) and 4-aminomethyl-3,3-dimethyloxindole (653 mg, 2.88 mmol) and stirred for 30 min at RT. The reaction mixture is washed with dil. ammonium chloride solution and water, the organic phase is dried on sodium sulphate, filtered, evaporated down and crystallised with water.

[0194] The bromine analogue **B-2** is prepared analogously starting from 5-bromo-2,4-dichloropyrimidine.

Table 3

Intermediate	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
B-1		0.84	337.0	C
B-2				

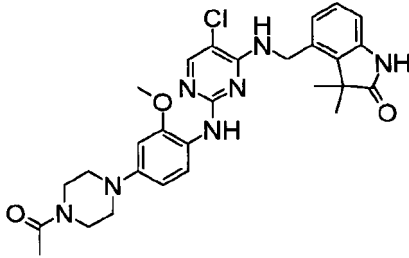
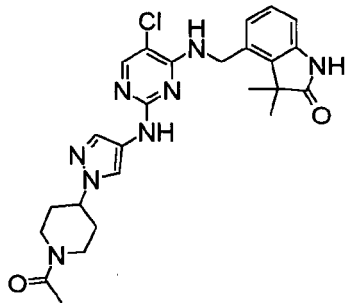
### 2.1.2 General synthesis of intermediates/example compounds C1 or (I) starting from intermediates B (method G).

**[0195]** A mixture of the corresponding 2-chloropyrimidine **B** (0.22 mmol), the (hetero)aromatic amine  $R^2\text{-NH}_2$  (0.29 mmol) and methanesulphonic acid (0.77 mmol) is stirred for 18 h in anhydrous 2-propanol (400  $\mu\text{L}$ ) at 90°C. The reaction mixture is purified by preparative HPLC-MS. The fractions containing the reaction product are freeze-dried.

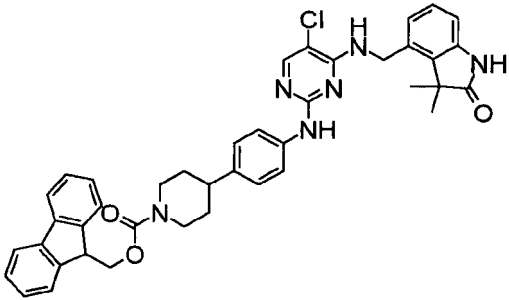
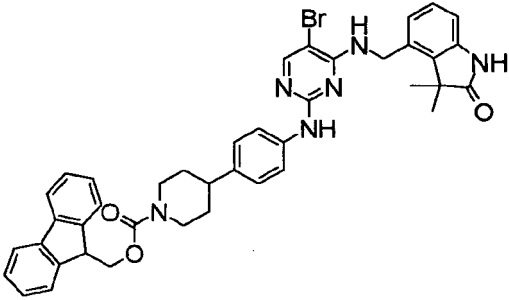
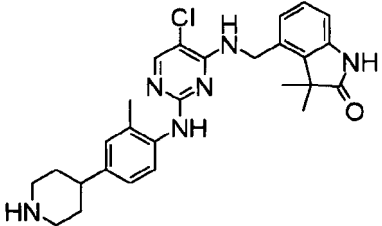
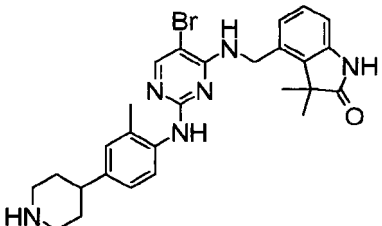
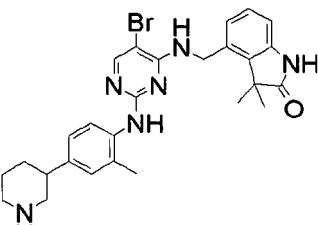
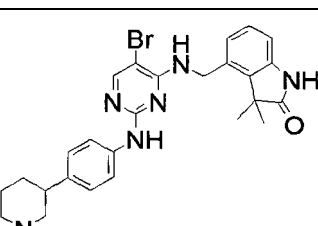
**[0196]** Instead of methanesulphonic acid p-toluenesulphonic acid or trifluoroacetic acid may be used. Instead of 2-propanol, 4-methyl-2-pentanol may be used as solvent. If the amine used,  $R^2\text{-NH}_2$ , has a BOC protective group this is cleaved *in situ* under the acidic reaction conditions.

**[0197]** The following intermediates/example compounds **C1** or **(I)** are prepared by this method (Table 4):

Table 4

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C1-1 (I-1)		0.68	550.2	C
C1-2 (I-2)		1.47	509.3	G

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C1-3 <sup>1</sup> (I-3)		2.30	699	K
C1-4 <sup>1</sup> (I-4)		2.20	743	I
C1-5 <sup>2</sup> (I-5)		1.40	535	G
C1-6 <sup>2</sup> (I-6)		1.60	491	L
C1-7 <sup>2,3</sup> (I-7)		1.91	535.2/53 7.3	G
C1-9 <sup>2,3</sup> (I-238)		1.33	521/523	P

5  
10  
15  
20  
25  
30  
35  
40  
45  
50  
55

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C1-16 <sup>2,3</sup> (I-245)		1.65	549/551	N
C1-17 <sup>2,3</sup> (I-246)		1.62	507/509	O
C1-18 <sup>2,3</sup> (I-247)		1.59	491/493	O
C1-19 <sup>2</sup> (I-248)		1.75	508/510	O
C1-20 <sup>2</sup> (I-249)		1.21	492/494	P
C1-21 <sup>2</sup> (I-250)		1.04	491/493	P

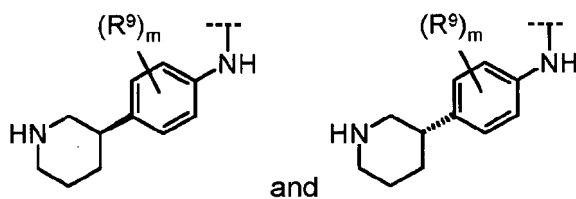


(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C1-22 <sup>2</sup> (I-251)		1.43	505/507	P
C1-23 <sup>2,3</sup> (I-252)		1.60	477/479	N
C1-24 <sup>2,3</sup> (I-253)		1.63	505/507	N
C1-25 <sup>2</sup> (I-254)		1.68	508/510	P
C1-26 <sup>2</sup> (I-255)		1.68	509/511	N
C1-27 <sup>2</sup> (I-256)		1.66	505/507	N

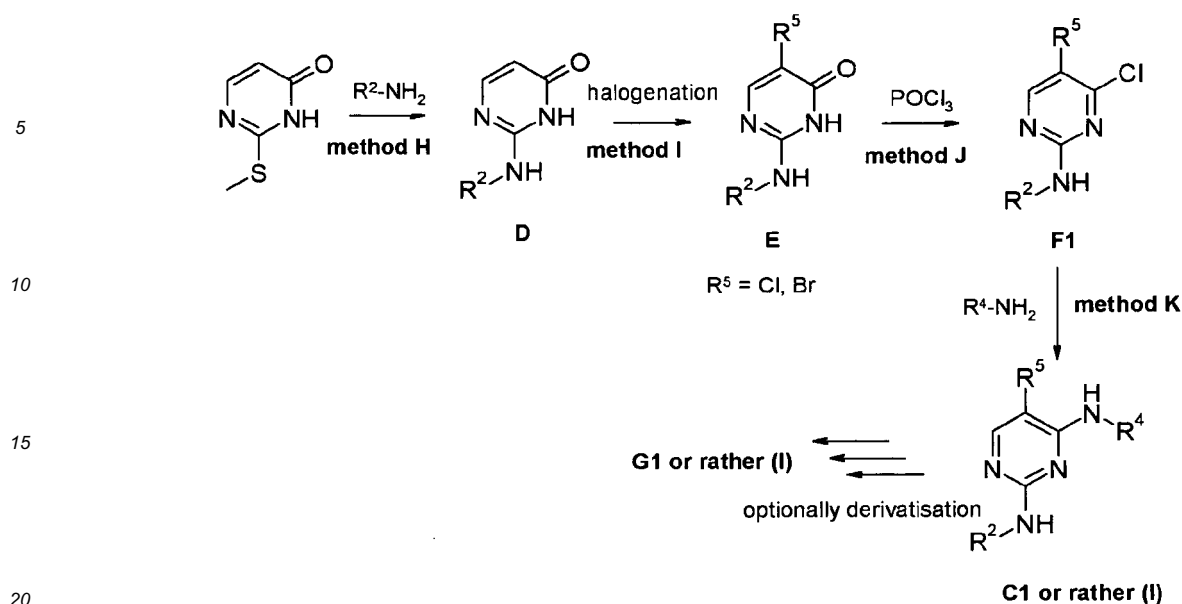
(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C1-28 <sup>2</sup> (I-257)		1.65	506/508	O
C1-29 <sup>2</sup> (I-258)		1.75	561/563	N
C1-30 <sup>2</sup> (I-259)		1.51	522/524	O
C1-31 <sup>2</sup> (I-260)		1.71	543/545	N
<sup>1</sup> cf. WO 2002/030927 <sup>2</sup> synthesis using a BOC-protected amine R <sup>2</sup> -NH <sub>2</sub> and cleaving <i>in situ</i> <sup>3</sup> racemic representation of the structural formula explicitly includes both configurations in each case, i.e.				



## 2.2 Variant 2

[0198]



### 2.2.1 Synthesis of intermediate D-1 (method H).

[0199] 2-methylsulphanyl-3*H*-pyrimidin-4-one (1.50 g, 10.55 mmol) and 4-(4-methylpiperazinyl)aniline (1.82 g, 9.50 mmol) in anhydrous NMP (5 mL) are stirred for 40 min at 210 °C in a microwave reactor. The reaction mixture is lyophilised and the residue is purified by chromatography.

Table 5

Intermediate	structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
D-1		0.49	286.2	B

### 2.2.2 Synthesis of intermediate E-1 (method I).

[0200] D-1 (910 mg, 3.19 mmol) in anhydrous acetic acid (5 mL) is combined at 0 °C with bromine (180  $\mu\text{L}$ , 3.51 mmol) in anhydrous acetic acid (5 mL) and stirred for 60 min at rt. The precipitated solid is isolated by filtration.

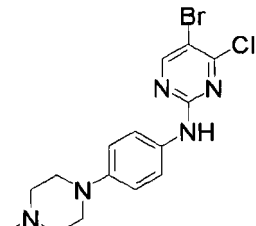
Table 6

Intermediate	structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
E-1		0.51	364/366	B

## 2.2.3 Synthesis of intermediate F1-1 (method I).

[0201] E-1 (780 mg, 2.14 mmol) in phosphorus oxychloride (8 mL) is stirred for 30 min at boiling temperature. The mixture is cooled to 0°C, dropped onto ice, neutralised with saturated potassium carbonate solution and exhaustively extracted with DCM. The organic phase is washed with water, dried on sodium sulphate, filtered and evaporated down.

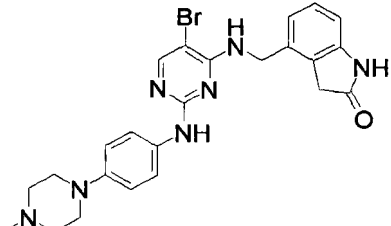
Table 7

Intermediate	structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
F1-1		1.05	382/384	B

## 2.2.4 Synthesis of Example compound I-8 (C1-8) (method I).

[0202] A mixture of F1-1 (70 mg, 0.18 mmol), N-ethyldiisopropylamine (0.64 mmol) and 4-aminomethyl-1,3-dihydroindol-2-one (38 mg, 0.19 mmol) is stirred in anhydrous NMP (400 µL) for 10 min at 120°C in a microwave reactor (Synthos 3000 made by Anton Paar, Rotor 4x24MG5). The reaction mixture is purified by preparative HPLC-MS. The fractions containing the reaction product are freeze-dried.

Table 8

Example	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-8 (C1-8)		1.54	508.3/ 510.3	C

## 2.3 Derivatisation of intermediates/example compounds C1 or (I) to form other intermediates/example compounds G1 or (I).

## 2.3.1 Fmoc cleaving (method J)

[0203] The Fmoc-protected compound C1 (e.g. C1-3 or C1-4) is combined with piperidine (5 equiv.) in DMF (10 mL/1 g of starting compound) and stirred for 1 h at rt. The mixture is evaporated down and the crude product is purified by column chromatography.

[0204] The following components G1 are obtained (Table 9):

Table 9

Intermediate (Example)	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G1-1 (I-9)		C1-3	1.39	477	K
G1-2 (I-10)		C1-4	1.43	521	K

### 2.3.2 Amide cleaving/deacetylation (method K)

**[0205]** C1-1 (1.22 g, 2.22 mmol) is stirred in conc. HCl (0.5 mL) for 15 min at 120°C in a microwave reactor. The reaction mixture is made basic with concentrated ammonia, diluted with water and exhaustively extracted with DCM. The organic phase is washed with water, dried on magnesium sulphate, filtered and evaporated down. The crude product is purified by column chromatography.

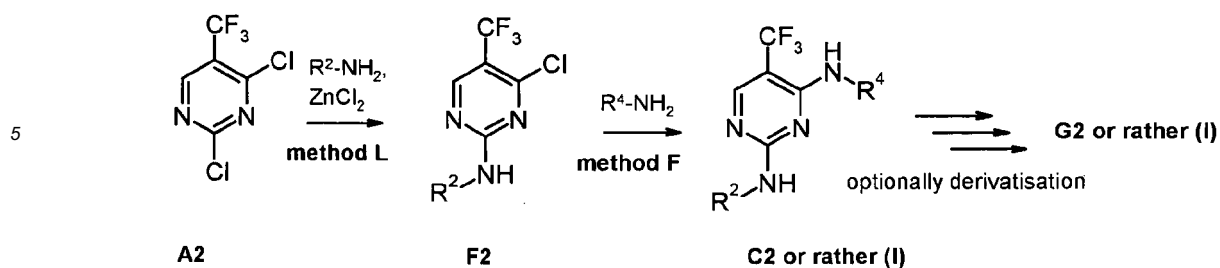
**[0206]** The following components **G1** are obtained (Table 10):

Table 10

Intermediate (Example)	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G1-3 (I-11)		C1-1	1.68	508	G
G1-4 (I-12)		C1-2	0.36	467.2	C

### 3. Preparation of the intermediates/example compounds C2 and G2 or (I)

**[0207]**



### 3.1 General synthesis of intermediates F2 (method L).

**[0208]** The preparation of 2-(hetero)arylamino-4-chloro-5-trifluoromethylpyrimidine derivatives **F2** is carried out analogously to WO 2005/023780. The crude products obtained are optionally purified by chromatography.

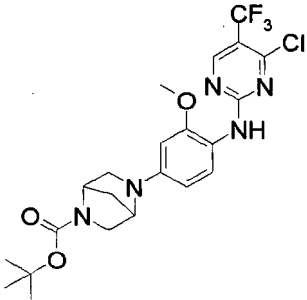
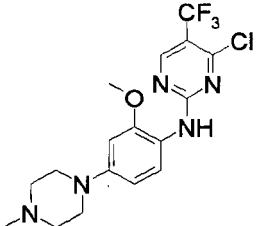
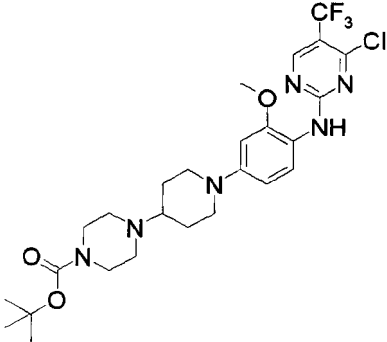
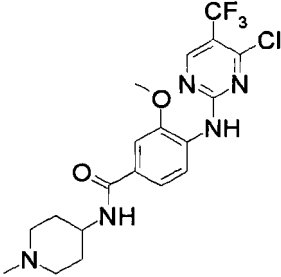
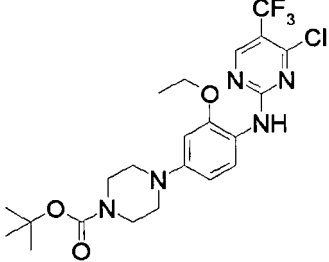
**[0209]** The following components **F2** are obtained (Table 11):

Table 11

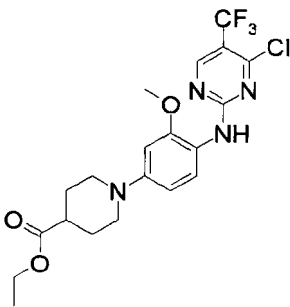
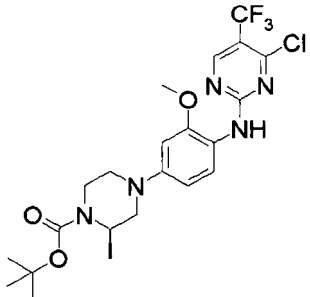
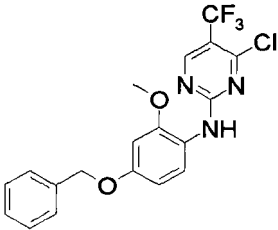
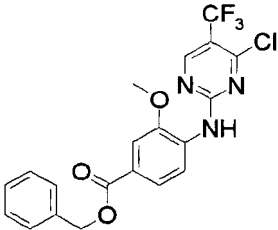
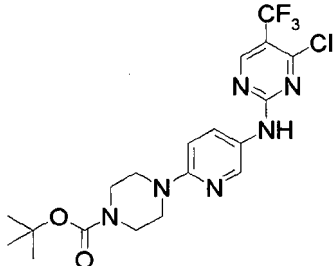
Intermediate	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
<b>F2-14</b>		1.50	488.1	C
<b>F2-25</b>		0.95	549.0	C
<b>F2-36</b>		1.24	445.2	C
<b>F2-47</b>		1.68	516.2	C

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(continued)

Intermediate	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
F2-5 <sup>8</sup>		1.49	500.2	C
F2-6 <sup>9</sup>		1.09	401.4	B
F2-7 <sup>10</sup>		1.21	571.2	B
F2-8 <sup>11</sup>		0.83	444.0	C
F2-9 <sup>12</sup>		1.58	502.2	C

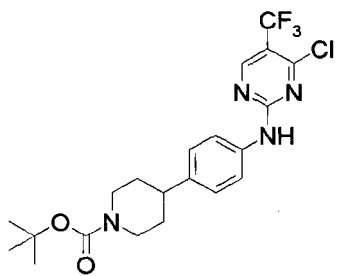
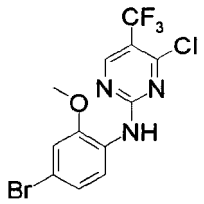
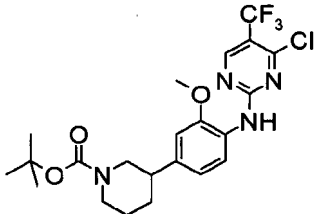
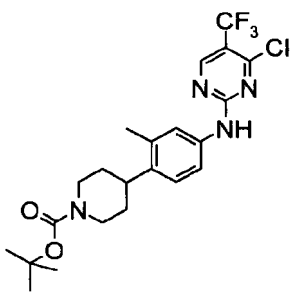
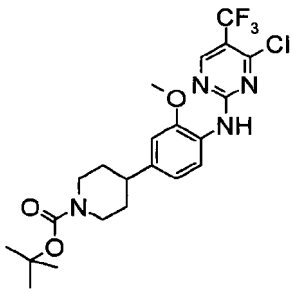
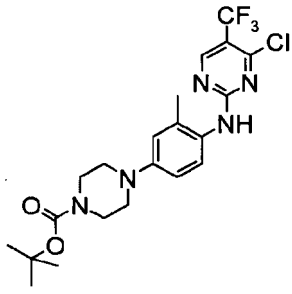
(continued)

Intermediate	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
F2-10 <sup>13</sup>		1.37	459.2	C
F2-11 <sup>8</sup>		1.59	502.2	C
F2-12 <sup>14</sup>		2.51	410	I
F2-13				
F2-14		2.2	459	I



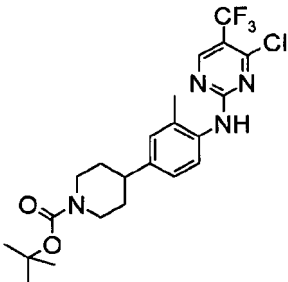
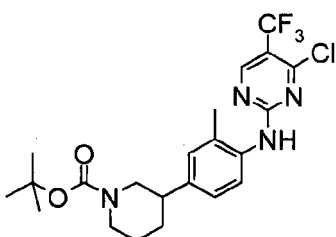
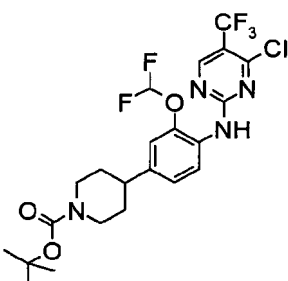
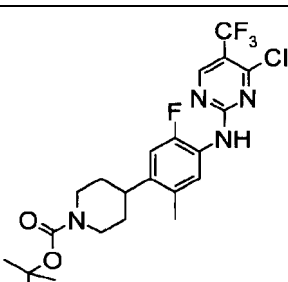
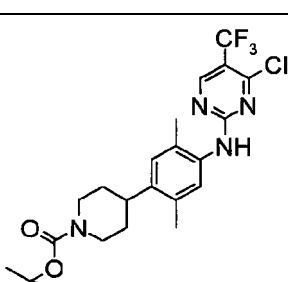
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(continued)

Intermediate	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
F2-15 <sup>15</sup>		2.61	401	I
F2-16				
F2-19 <sup>15,16</sup>		2.03	431	O
F2-20 <sup>15</sup>		2.50	469 (M-H)	P
F2-21 <sup>15</sup>		2.02	431 (M+H-tBu)	O
F2-22 <sup>7</sup>		1.91	472	O

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(continued)

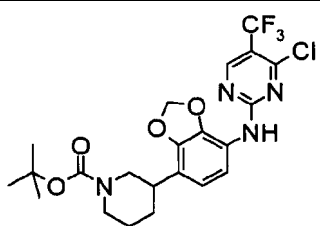
Intermediate	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
F2-23 <sup>15</sup>		1.61	469 (M-H)	O
F2-24 <sup>15,16</sup>		243	469 (M-H)	P
F2-25 <sup>15</sup>		2.13	521 (M-H)	N
F2-26 <sup>16</sup>		2.13	487 (M-H)	N
F2-27 <sup>15</sup>		2.14	483 (M-H)	N

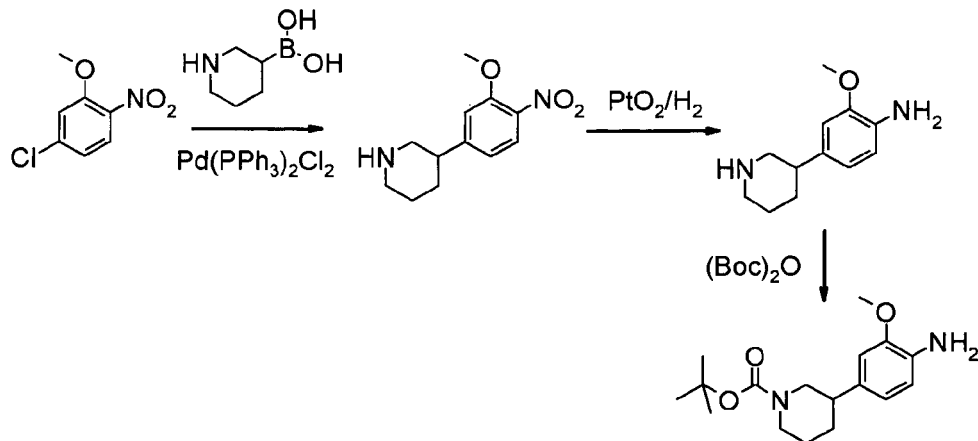
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(continued)

Intermediate	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
F2-28 <sup>15</sup>		1.97	483 (M-H)	O
F2-29 <sup>15</sup>		2.15	429 (M+H)-tBu	N
F2-30 <sup>15</sup>		1.94	445 (M+H)-tBu	O
F2-31				
F2-32				

(continued)

Intermediate	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
<b>F2-33</b>				
<p><sup>4</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared from the nitro compound analogously to WO 2006/021548 by reduction using standard methods</p> <p><sup>5</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared according to US 2008/300242</p> <p><sup>6</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared analogously to WO 2002/006232</p> <p><sup>7</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared analogously to US 2008/300242</p> <p><sup>8</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared from 4-fluoro-2-methoxy-1-nitrobenzene analogously to WO 2006/021548 using standard methods</p> <p><sup>9</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared according to WO 2006/021548</p> <p><sup>10</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared analogously to WO 2005/016894</p> <p><sup>11</sup> <b>F2-10</b> is prepared from the corresponding aminobenzoic acid (cf. WO 2007/115999) by reaction with thionyl chloride and 1-methylpiperidin-4-amine using standard methods</p> <p><sup>12</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared from 2-ethoxy-4-fluoro-1-nitrobenzene analogously to WO 2006/021548 using standard methods</p> <p><sup>13</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared from 4-fluoro-2-methoxy-1-nitrobenzene and ethyl piperidine-4-carboxylate analogously to WO 2006/021548 using standard methods</p> <p><sup>14</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared from the corresponding nitro compound by reduction</p> <p><sup>15</sup> the educt aniline R<sup>2</sup>-NH<sub>2</sub> is prepared according to or analogously to the following method:</p>				



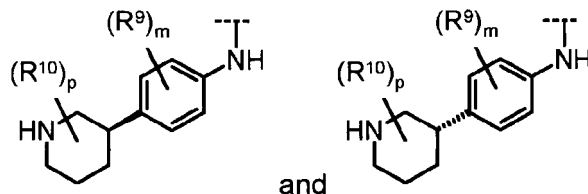
**[0210]** 4-chloro-2-methoxy-nitrobenzene (2.0 g, 9.6 mmol) is taken up in 40 mL anhydrous dioxane in an argon atmosphere. 3-pyridineboric acid (1.77 g, 14.4 mmol) is added to this mixture, followed by degassed sodium carbonate solution (10 mL, 3 M) and bis-triphenylphosphine-palladium (II) chloride (337 mg, 48 mmol). The reaction mixture is stirred for 16 h at 80°C under an argon atmosphere. After further addition of sodium carbonate (3.2 g) and 0.1 eq palladium catalyst the mixture is stirred again for 4 h at 85 °C. After cooling, the reaction mixture is poured onto water (100 mL), extracted 3 x with ethyl acetate (20 mL aliquots), the combined organic phases are dried on magnesium sulphate and evaporated down in vacuo. Chromatographic purification through silica gel with cyclohexane/ethyl acetate yields the coupling product.

**[0211]** The coupling product obtained (2.04 g, 8.63 mmol) is taken up in glacial acetic acid (100 mL), mixed with platinum oxide (100 mg, 0.1 eq) and hydrogenated for 48 h at rt and 9 bar of H<sub>2</sub> pressure. The reaction mixture is filtered through Celite, the volatile constituents are eliminated in vacuo and the solution obtained is poured into saturated, aqueous sodium hydrogen carbonate solution (50 mL). It is extracted 3 x with ethyl acetate (30 mL aliquots), the combined

organic phases are dried on magnesium sulphate, then after evaporation purified by chromatography (silica gel, cyclohexane/ethyl acetate) and the aniline is obtained.

[0212] The aniline obtained (971 mg, 4.71 mmol) is taken up in dichloromethane (50 mL), di-*tert*-butylcarbonate (1.03 g, 4.71 mmol) is added and the reaction mixture is stirred for 3 h at rt. After concentration in vacuo the crude product of the Boc-protected aniline is obtained, which is further used directly.

[0213] <sup>16</sup> racemic representation of the structural formula always explicitly includes both configurations, *i.e.*



### 3.2 Derivatisation of intermediates F2 to form further intermediates F2.

#### 3.2.1 Synthesis of intermediate F2-17 (Boc cleaving, method M)

[0214] F2-17 (200 mg, 0.43 mmol) in anhydrous DCM (5 mL) is combined at 0°C with TFA (30 equivalents) and stirred for 2 h at RT. The mixture is mixed with water, neutralised with 2 N NaOH and exhaustively extracted with DCM. The organic phase is washed with water, dried on magnesium sulphate, filtered and evaporated down.

#### 3.2.2 Synthesis of intermediate F2-18 (reductive amination, method N)

[0215] F2-17 (156 mg, 0.43 mmol) in anhydrous DCM (10 mL) is combined with 37 % aqueous formaldehyde solution (1.2 equivalents) and acetic acid (2.4 equivalents) and stirred for 30 min at rt. Sodium triacetoxyborohydride (1.4 equivalents) is added. The reaction mixture is stirred for 16 h and then evaporated down. The residue is taken up in EtOAc, washed with saturated sodium hydrogen carbonate solution and saturated saline solution, dried on magnesium sulphate, filtered and evaporated down. The crude product is optionally purified by column chromatography.

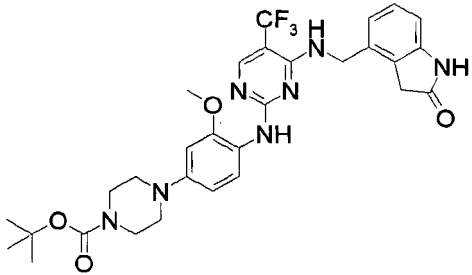
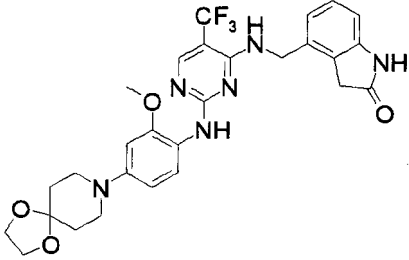
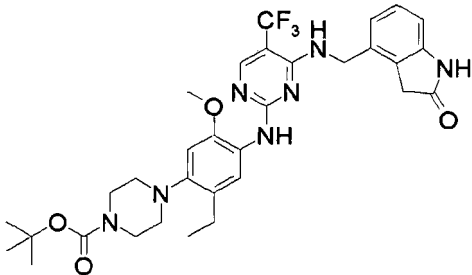
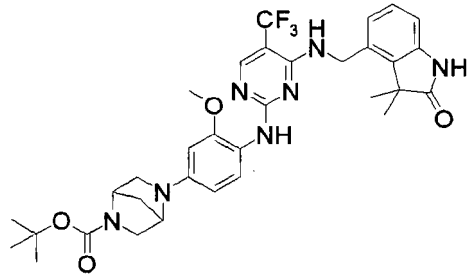
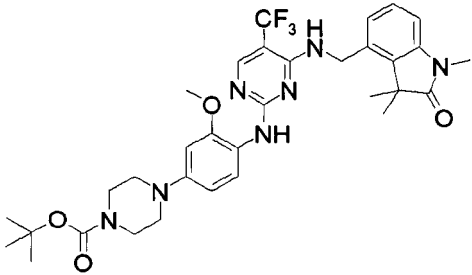
Table 12

Intermediate	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
F2-17		1.5	359	I
F2-18		1.53	373	I

### 3.3 General synthesis of intermediates/example compounds C2 or (I) starting from intermediates F2 (method F).

[0216] The reaction of 4-chloropyrimidine components F2 with corresponding amines R<sup>4</sup>-NH<sub>2</sub> is carried out according to method F (cf. 2.1.1)

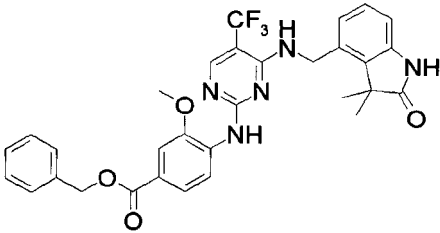
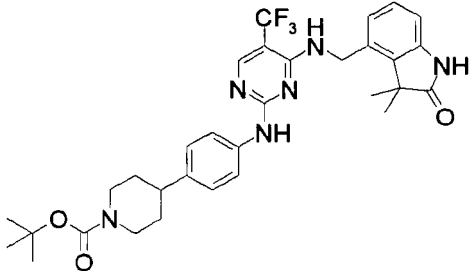
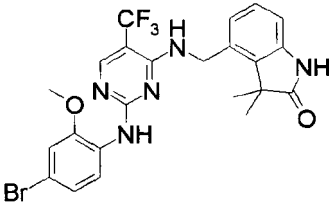
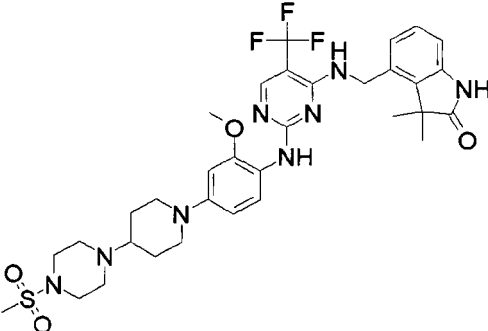
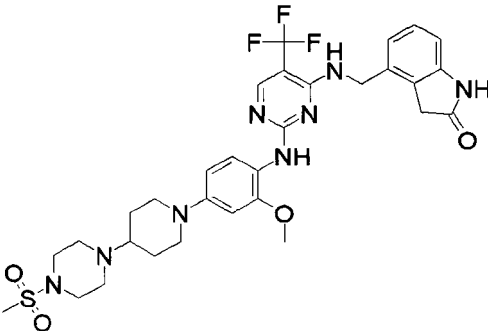
Table 13

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C2-1 (I-13)		1.11	614.4	C
C2-2 (I-14)		0.82	571.2	C
C2-3 (I-15)		1.35	642.4	C
C2-4 (I-16)		1.17	654.4	C
C2-5 (I-17)		1.35	656.4	C

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C2-6 (I-18)		1.22	642.3	C
C2-7 (I-19)		1.31	656.4	C
C2-8 (I-20)		1.14	628.4	C
C2-9 (I-21)		1.10	613.4	C
C2-10 (I-22)		2.13	546	I

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C2-11 (I-23)		2.41	592	K
C2-12 (I-24)		2.24	611	I
C2-13		1.30	536.2/538.2	C
C2-14 (I-25)		1.87	703.3	G
C2-15 (I-26)		1.76	675.3	G



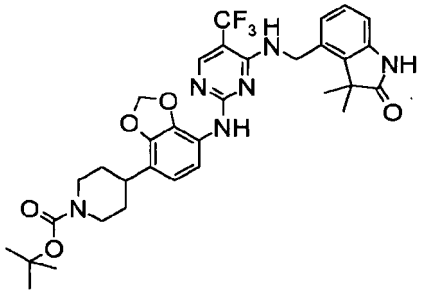
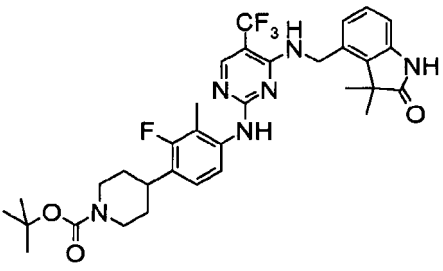
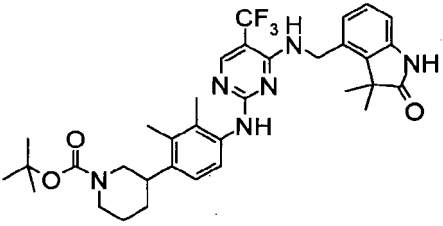
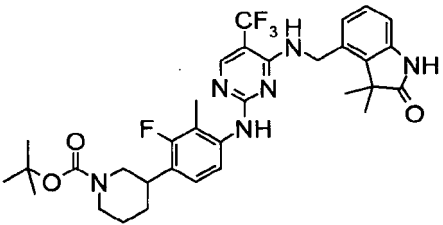
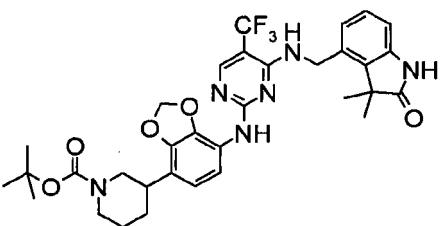
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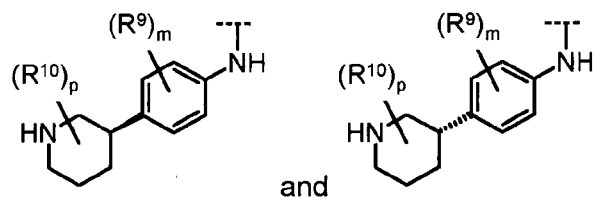
Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C2-16 <sup>17</sup> (I-261)		1.92	641	O
C2-17 (I-262)		1.61	625	P
C2-18 (I-263)		1.81	626	O
C2-19 (I-264)		1.99	625	N
C2-20 <sup>17</sup> (I-265)		2.24	625	P

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C2-21 (I-266)		2.03	677	N
C2-22 (I-267)		2.03	643	N
C2-23 (I-268)		2.02	639	N
C2-24 (I-269)		1.87	639	O
C2-25 (I-270)		2.03	639	N

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
C2-26 (I-271)		1.83	655	O
C2-27 (I-272)				
C2-28 (I-273)				
C2-29 (I-274)				
C2-30 (I-275)				
17 racemic representation of the structural formula always explicitly includes both configurations, <i>i.e.</i>				



## 10

## 15

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(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
G2-6 (I-32)		1.74	528.3	G
G2-7 (I-33)		1.90	556.3	G
G2-8 (I-34)		0.70	556.4	C
G2-9 (I-35)		1.52	511	I
G2-156 <sup>18</sup> (I-276)		1.67	541	O
G2-157 (I-277)		1.58	525	P

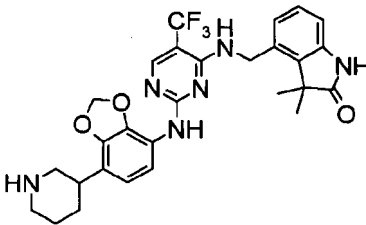
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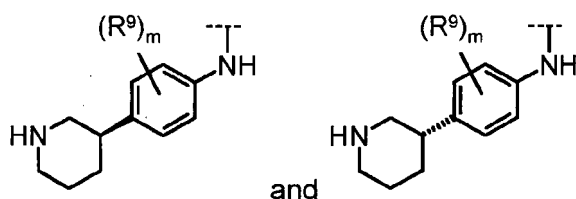
Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
G2-158 (I-278)		1.59	526	O
G2-159 (I-279)		1.17	525	P
G2-160 <sup>18</sup> (I-280)		1.71	525	O
G2-161 (I-281)		1.77	577	N
G2-162 (I-282)		1.72	543	N
G2-163 (I-283)		1.72	539	N

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
G2-164 (I-284)		1.69	539	O
G2-165 (I-285)		1.82	539	N
G2-166 (I-286)		1.66	555	O
G2-167 (I-287)				
G2-168 (I-288)				
G2-169 (I-289)				

(continued)

Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
G2-170 (I-290)				
<sup>18</sup> racemic representation of the structural formula always explicitly includes both configurations, <i>i.e.</i>				

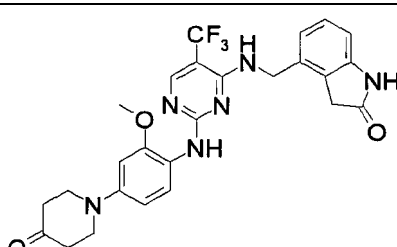
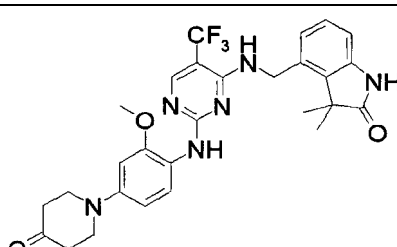


### 3.4.2 Ketal cleaving (method Q)

**[0219]** C2-2 (1.20 g, 2.10 mmol) in 6 N HCl (10 mL) and MeOH (5 mL) is stirred for 18 h at rt. After the addition of 1.5 mL concentrated HCl the mixture is stirred for a further 2 h at rt. The reaction mixture is made basic with concentrated ammonia, diluted with water and exhaustively extracted with DCM. The organic phase is washed with water, dried on magnesium sulphate, filtered and evaporated down. The crude product is optionally purified by column chromatography.

**[0220]** The following components G2 (Table 15) are prepared by this method:

Table 15

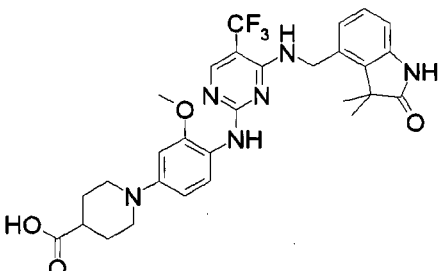
Intermediate (Example)	Structure	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
G2-10 (I-36)		0.93	527.0	B
G2-11 (I-37)		0.90	555.2	C

### 3.4.3 Alkylester cleavage (method R)

**[0221]** C2-9 (320 mg, 0.52 mmol) in THF (2 mL) and EtOH (0.5 mL) is combined with 1 N NaOH (3 equiv.) and stirred for 16 h at rt. The reaction mixture is neutralised with 1 N HCl, evaporated down to one third of the volume and divided between water and DCM. The aqueous phase is exhaustively extracted with DCM. The combined organic phase is washed with water, dried on magnesium sulphate, filtered and evaporated down. The crude product is optionally purified by column chromatography.



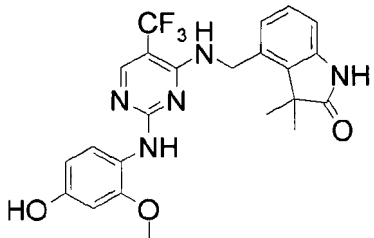
Table 16

Intermediate (Example)	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G2-12 (I-38)		0.83	585.4	C

### 3.4.4 Debenzylation (method S)

[0222] C2-10 (155 mg, 0.27 mmol) is hydrogenated in the presence of Pd(OH)<sub>2</sub> in EtOH (6.5 mL) 16 h at rt under a hydrogen pressure of 1 bar. The reaction mixture is filtered and the filtrate is evaporated down.

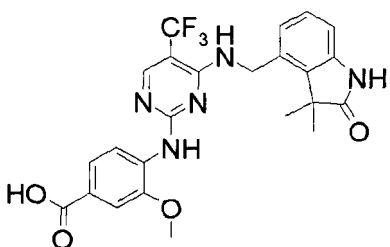
Table 17

Intermediate	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G2-13		1.6	474	I

### 3.4.5 Benzylester cleavage (method T)

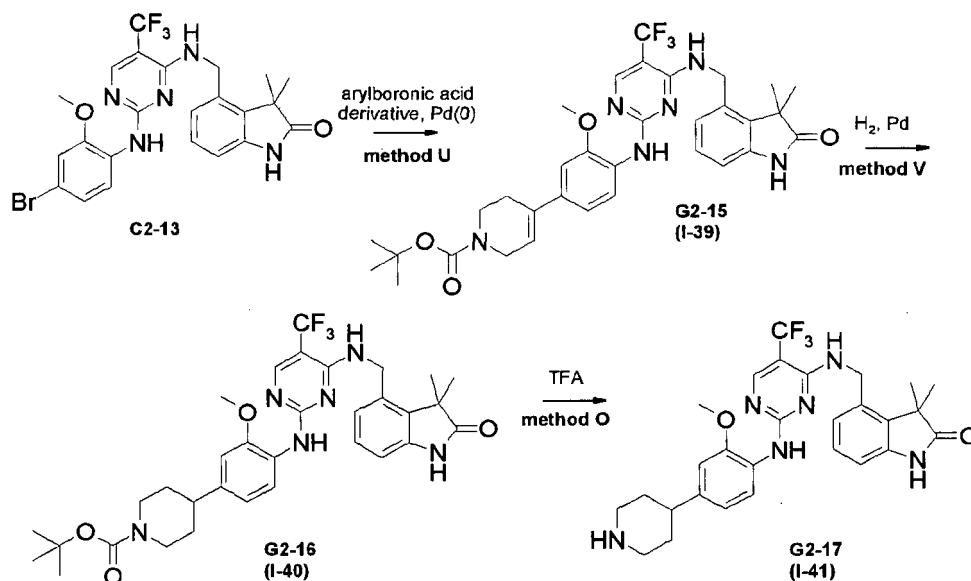
[0223] Benzylester cleavage on C2-11: The benzylester cleavage is carried out analogously to the debenzylation (method S, 3.4.4).

Table 18

Intermediate	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G2-14		1.89	502	K

### 3.4.6 by Suzuki coupling

[0224]



### 3.4.6.1 Suzuki reaction (method U)

**[0225]** *N*-Boc-1,2,5,6-tetrahydropyridine-4-boric acid pinacol ester (192 mg, 0.60 mmol), **C2-13** (268 mg, 0.50 mmol), bis(triphenylphosphine)palladium(II)chloride (36 mg, 0.03 mmol) and sodium carbonate (159 mg, 1.5 mmol) are stirred in water (1.5 mL) and dioxane (3 mL) under argon for 20 min at 120°C in a microwave reactor. The reaction mixture is combined with EtOH (80 mL), filtered and used directly in the next step.

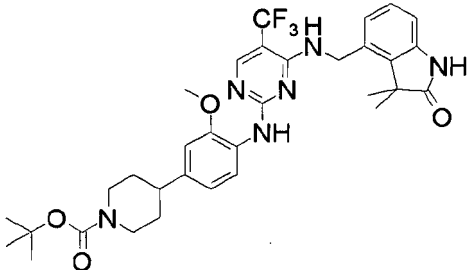
Table 19

Intermediate (Example)	Structure	<i>t</i> <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G2-15 (I-39)		1.47	639.4	C

### 3.4.6.2 Reduction/hydrogenation (method V)

**[0226]** The reaction mixture from the previous step is hydrogenated in the H-Cube throughflow reactor (Thalos Nano, 40°C, flow: 1 mL/min, Full H<sub>2</sub> Mode, catalyst: 10 % Pd/C). The reaction mixture is evaporated down.

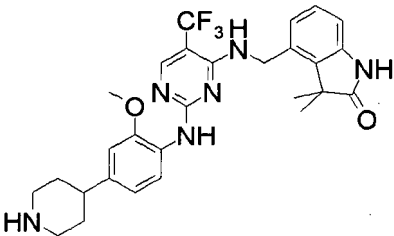
Table 20

Intermediate (Example)	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G2-16 (I-40)		1.43	641.4	C

#### 3.4.6.3 Boc cleaving (cf. method O, 3.4.1)

[0227] The cleaving der Boc-protective group is carried out analogously to **method O**.

Table 21

intermediate (Example)	Structure	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
G2-17 (I-41)		2.25	541.3	G

### 4. Preparation of further Example compounds (I) by derivatisation of Example compounds/intermediates C1 or C2, G1 or G2 and (I)

#### 4.1 Acylation

##### 4.1.1 General synthesis: acylation with acid chlorides (method W)

[0228] The corresponding compound C1, C2, G1 or G2 is taken up in anhydrous DCM, combined with the acid chloride (1.4 equivalents) and triethylamine (3 equivalents) and stirred for 3 h at rt. The reaction mixture is evaporated down, the residue is taken up in DMSO and purified by preparative HPLC-MS. The fractions containing the reaction product are freeze-dried.

##### 4.1.2 General synthesis: amide coupling with acids (method X)

[0229] The starting compound (50 mg) in anhydrous DMSO (1 mL) is combined with TBTU (1.5 equivalents), triethylamine (1.5 equivalents) and the corresponding carboxylic acid (5 equivalents) and stirred for 5 h at rt. The reaction mixture is purified by preparative HPLC-MS. The fractions containing the reaction product are freeze-dried.

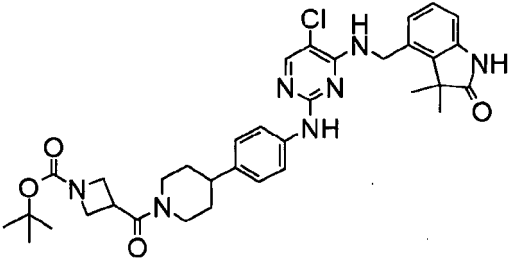
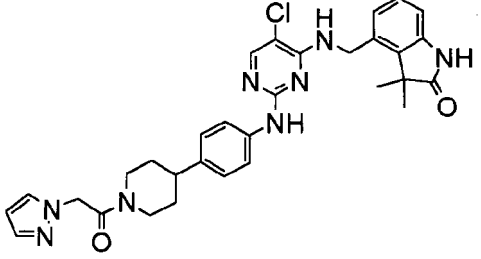
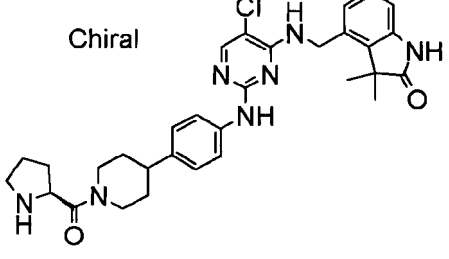
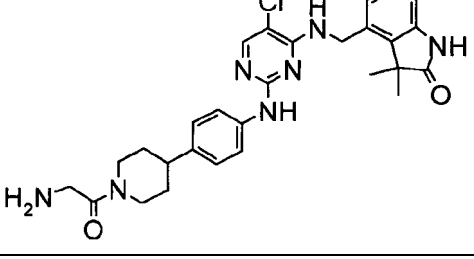
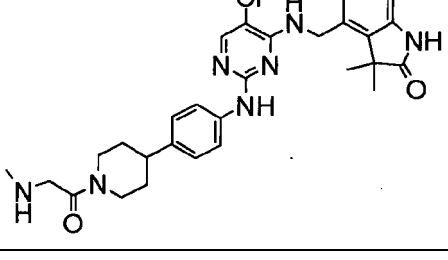
[0230] (Acid components which in turn contain a Boc-protected amino functionality are deprotected in a subsequent step by reacting with TFA or HCl.)

[0231] The following example compounds (Table 22) are obtained by acylation of corresponding precursors. The example compounds obtained first may be optionally be deprotected by conventional methods and/or reacted by further standard reactions (e.g. direct alkylation, reductive alkylation, carboxylic acid amide formation, sulphonamide formation, acylation etc.) to form other example compounds.

Table 22

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-42 (G1-5)		G1-2	2.75	608	H
I-43 (G1-6)		G1-1	2.7	562	H
I-44 (G1-7)	Chiral 	G1-1	3.59	674	H
I-45 (G1-8)		G1-1	3.47	635	H
I-46 (G1-9)		G1-1	3.56	648	H

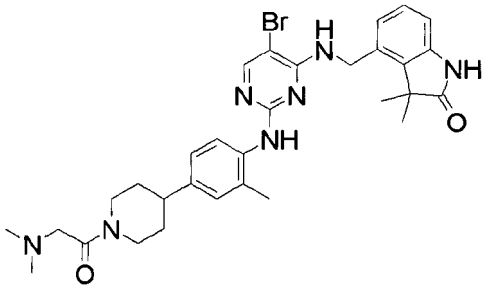
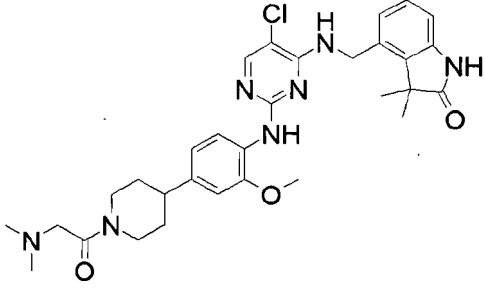
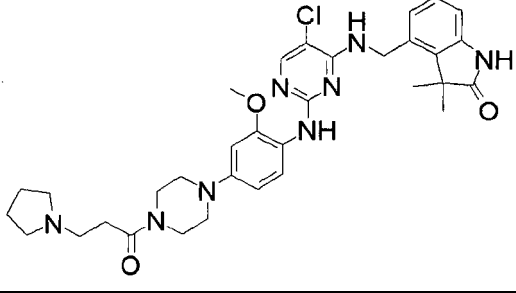
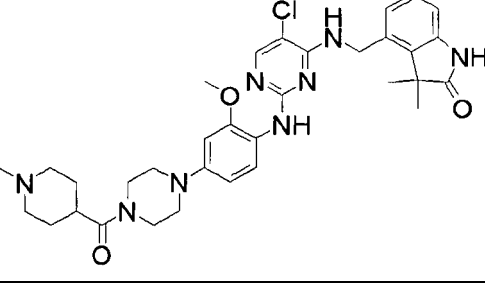
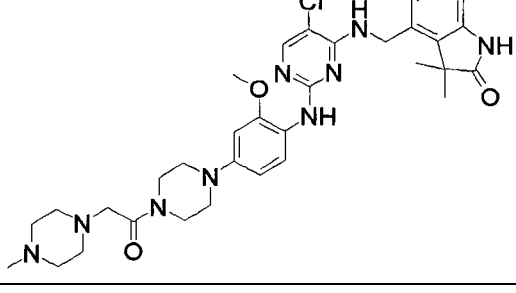
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-47 (G1-10)		G1-1	3.62	661	H
I-48 (G1-11)		G1-1	3.13	585	H
I-49 (G1-12)	Chiral 	G1-1	2.72	574	H
I-50 (G1-13)		G1-1	2.62	534	H
I-51 (G1-14)		G1-1	2.62	548	H

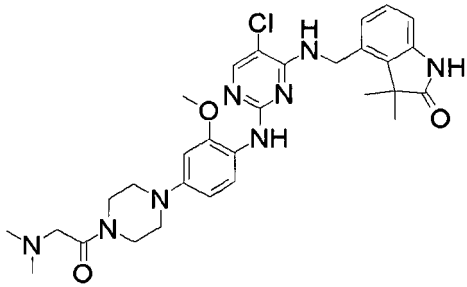
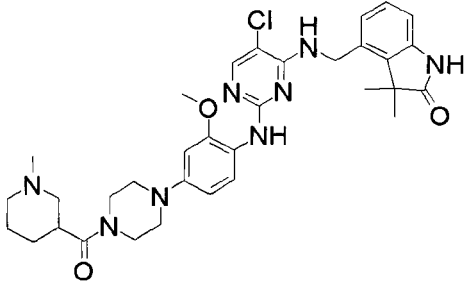
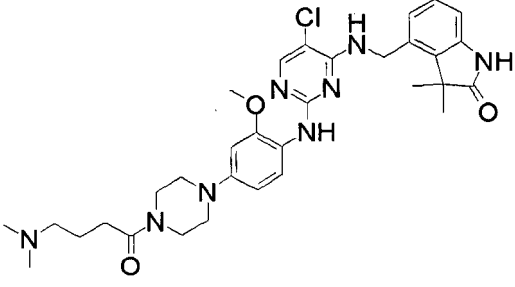
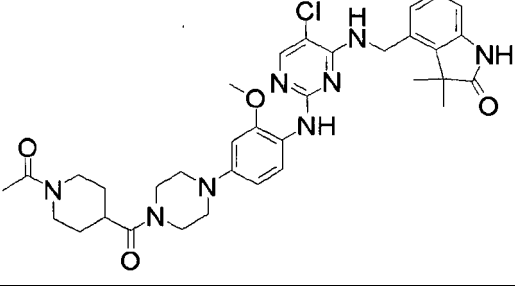
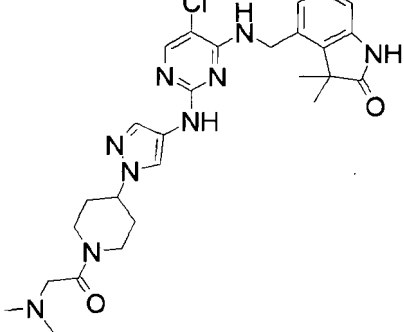
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-52 (G1-15)		G1-1	2.61	560	H
I-53 (G1-16)		G1-2	3.1	648	H
I-54 (G1-17)		G1-2	3.26	609	H
I-55 (G1-18)		G1-2	2.75	620	H
I-56 (G1-19)		G1-2	2.7	606	H

(continued)

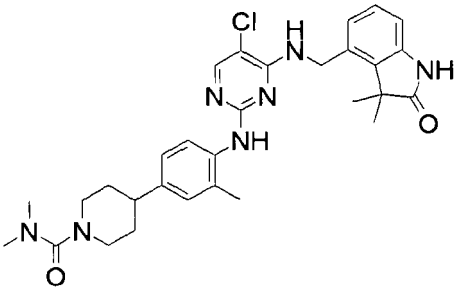
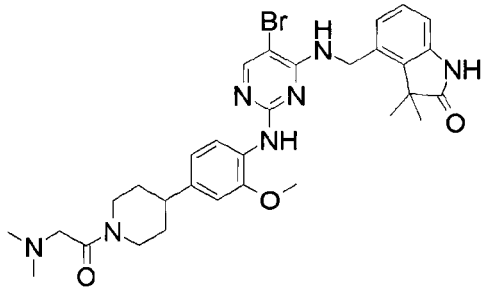
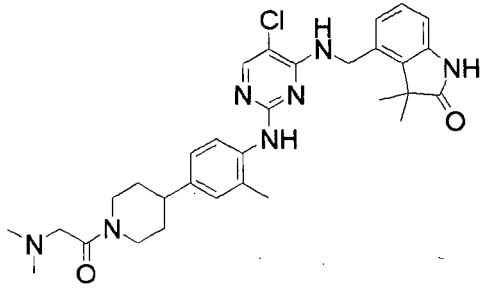
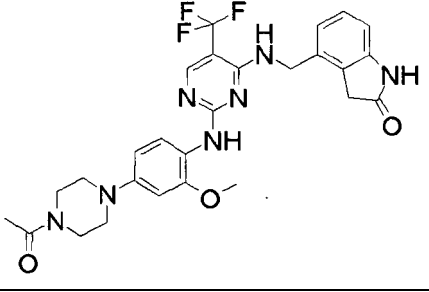
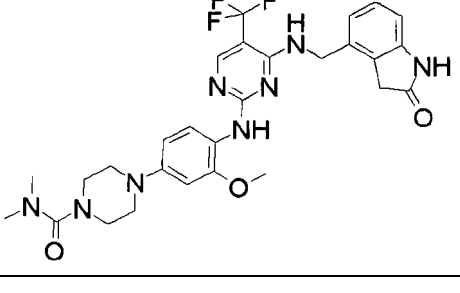
#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-57 (G1-20)		C1-6	1.87	620.2/ 622.2	G
I-58 (G1-21)			1.86	592.3	G
I-59 (G1-22)		G1-3	1.91	633.3	G
I-60 (G1-23)		G1-3	1.81	633.3	G
I-61 (G1-24)		G1-3	1.74	648.2	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-62 (G1-25)		G1-3	1.80	593.3	G
I-63 (G1-26)		G1-3	1.84	633.3	G
I-64 (G1-27)		G1-3	1.87	621.3	G
I-65 (G1-28)		G1-3	1.72	633.3	G
I-66 (G1-29)		G1-4	1.16	552.2	G



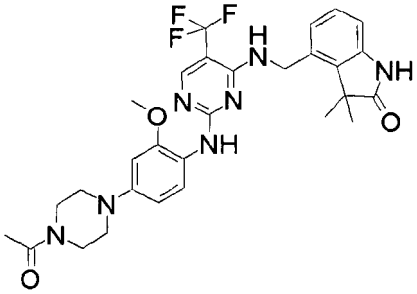
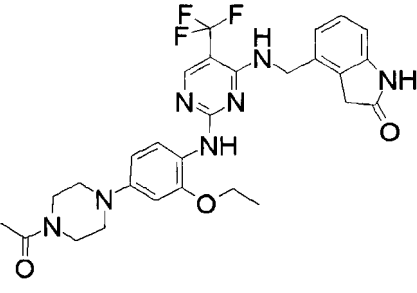
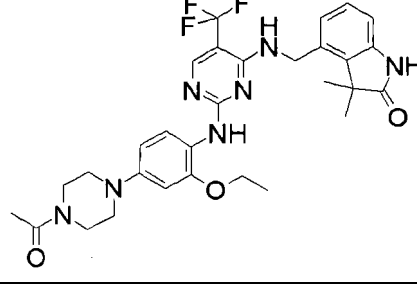
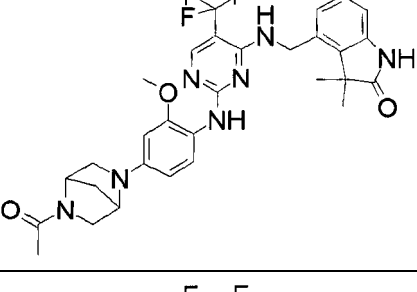
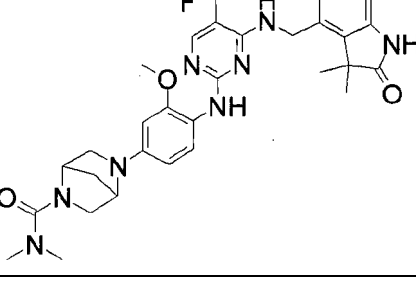
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#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-67 (G1-30)		C1-5	1.40	562.3	G
I-68 (G1-31)			1.90	636.2/ 638.3	G
I-69 (G1-32)		C1-5	1.37	576.2	G
I-70 (G2-18)		G2-1	1.64	556.3	G
I-71 (G2-19)		G2-1	1.74	585.3	G

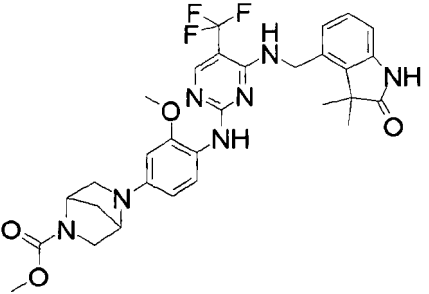
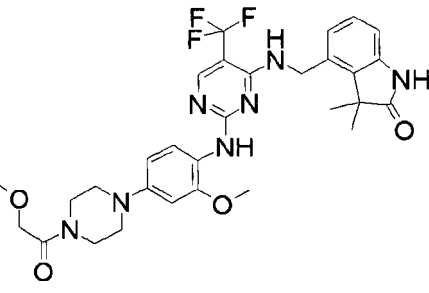
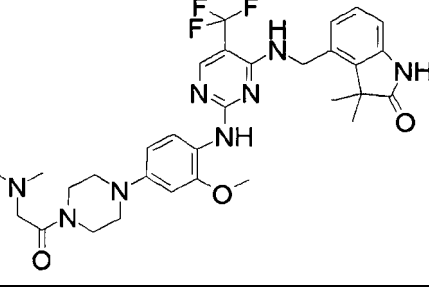
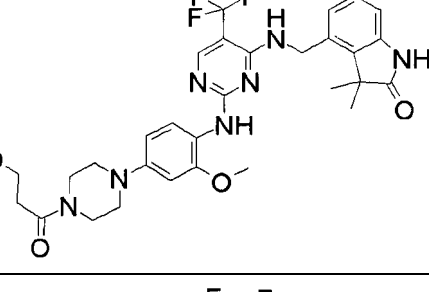
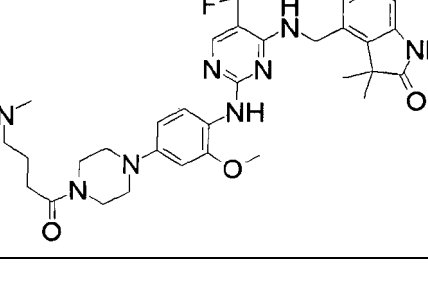
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#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-72 (G2-20)		G2-1	1.89	586.3	G
I-73 (G2-21)		G2-8	2.02	614.3	G
I-74 (G2-22)		G2-9	3.16	624	H
I-75 (G2-23)		G2-9	3.05	596	H
I-76 (G2-24)		G2-5	1.88	613.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-77 (G2-25)		G2-5	1.78	584.3	G
I-78 (G2-26)		G2-6	1.75	570.3	G
I-79 (G2-27)		G2-7	1.88	598.3	G
I-80 (G2-28)		G2-3	1.76	596	G
I-81 (G2-29)		G2-3	1.86	625.3	G

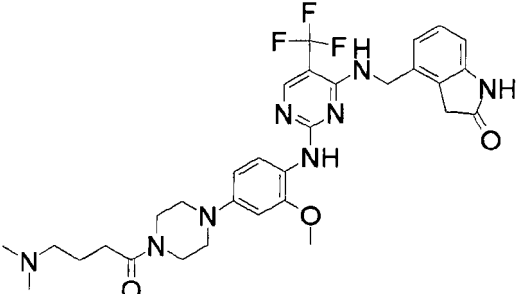
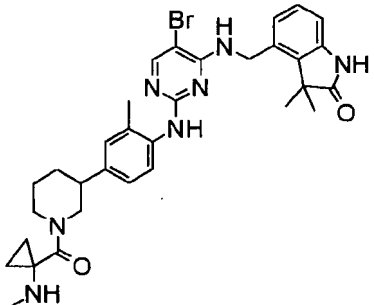
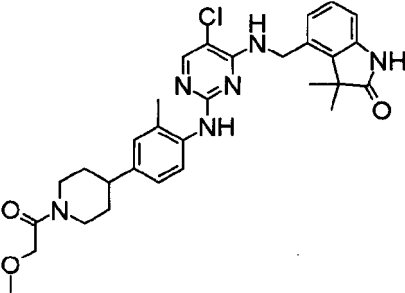
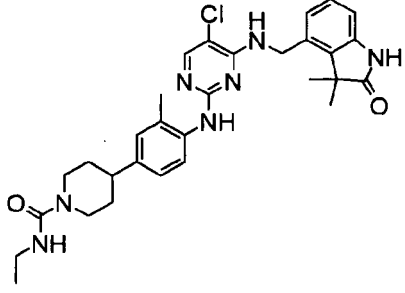
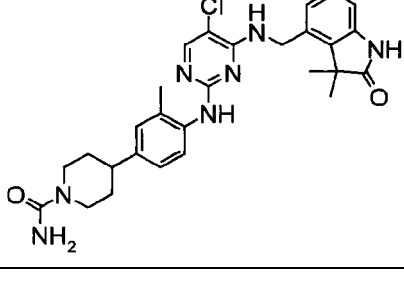
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#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-82 (G2-30)		G2-3	1.91	612.3	G
I-83 (G2-31)		G2-5	1.80	614.3	G
I-84 (G2-32)		G2-5	1.96	627.3	G
I-85 (G2-33)		G2-5	1.84	628	G
I-86 (G2-34)		G2-5	1.93	655.3	G

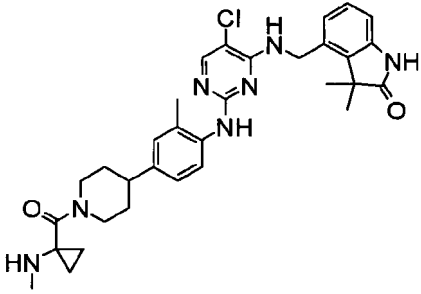
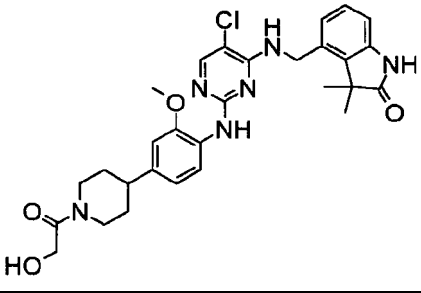
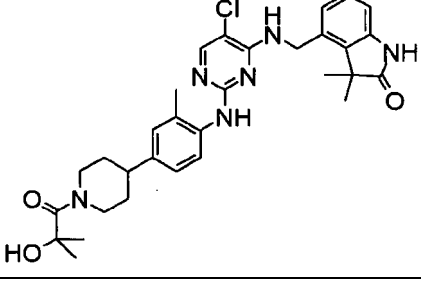
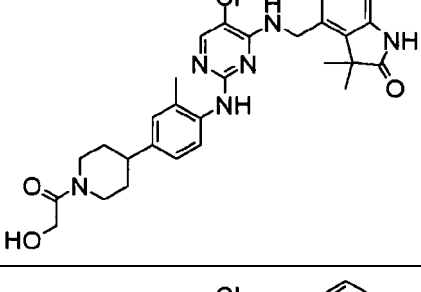
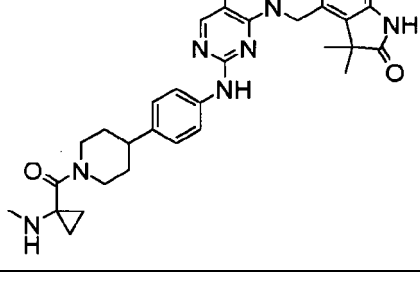
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-87 (G2-35)		G2-5	1.93	667.2	G
I-88 (G2-36)		G2-5	1.84	682.3	G
I-89 (G2-37)		G2-5	1.88	641.3	G
I-90 (G2-38)		G2-5	1.91	667.2	G
I-91 (G2-39)		G2-1	1.73	599.2	G

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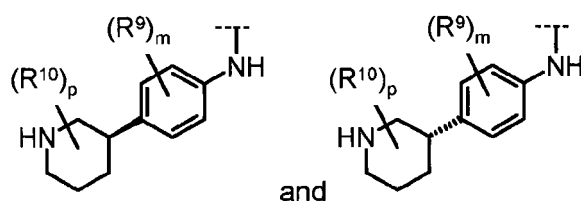
#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-92 (G2-40)		G2-1	1.82	627.2	G
I-291 <sup>19</sup> (G1-63)		C1-7	1.34	632/63 4	P
I-292 (G1-64)		C1-5	1.32	563/56 5	P
I-293 (G1-65)		C1-5	1.33	562/56 4	P
I-294 (G1-66)		C1-5	1.24	534/53 6	P

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-295 (G1-67)		C1-5	1.32	588/59 0	P
I-296 (G1-68)		C1-19	1.31	565/56 7	P
I-297 (G1-69)		C1-5	1.35	577/57 9	P
I-298 (G1-70)		C1-5	1.27	549/55 1	P
I-299 (G1-71)		G1-1	1.29	574/57 6	P

(continued)

#	Structure	educt	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
I-300 (G1-72)		C1-19	1.38	593/59 5	P
<sup>19</sup> racemic representation of the structural formula always explicitly includes both configurations, i.e.					



## 4.2 Reductive amination

### 4.2.1 General synthesis: Reductive amination on amines C1, C2, G1 or G2 (method Y)

**[0232]** The corresponding compound C1, C2, G1 or G2 is taken up in anhydrous NMP, combined with the carbonyl compound (3 equivalents) and sodium triacetoxyborohydride (2.9 equivalents) and stirred for 1.5 h at rt. The reaction mixture is combined with formic acid and purified by preparative HPLC-MS. The fractions containing the reaction product are freeze-dried.

**[0233]** The following Example compounds (Table 23) are obtained by reductive amination of the corresponding precursors. The Example compounds obtained first may optionally be deprotected by conventional methods and/or reacted by further standard reactions (e.g. direct alkylation, reductive alkylation, carboxylic acid amide formation, sulphonamide formation, acylation etc.) to form further Example compounds.

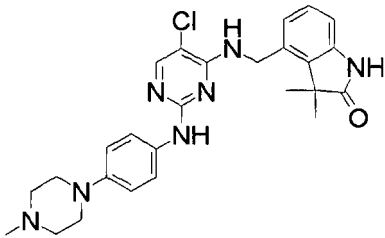
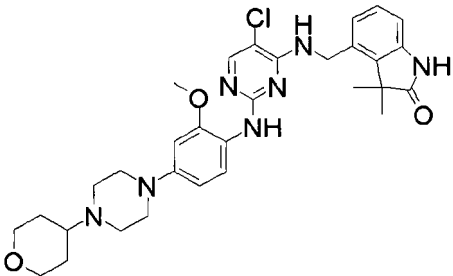
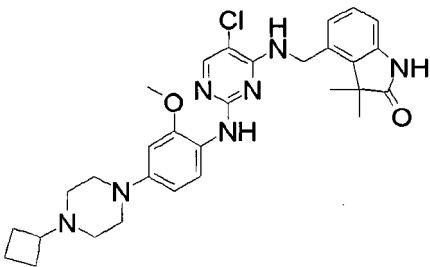
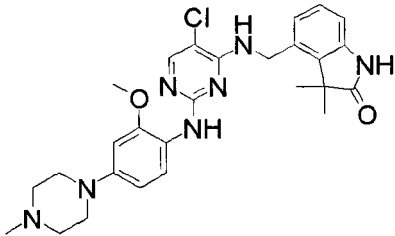
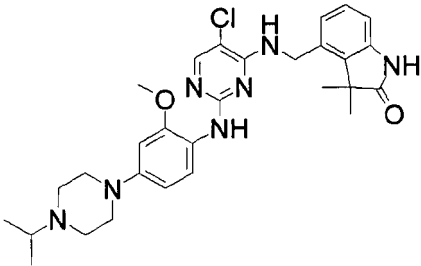
Table 23

#	Structure	educt	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
I-93 (G1-33)		G1-1	2.59	533	K



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(continued)

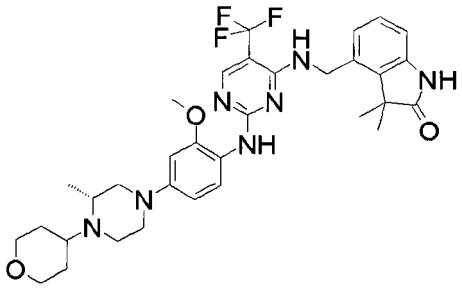
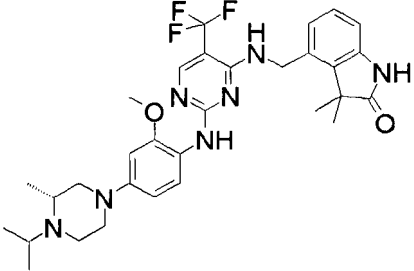
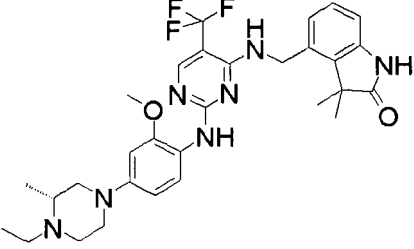
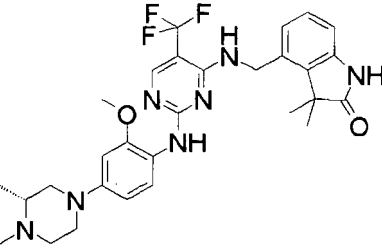
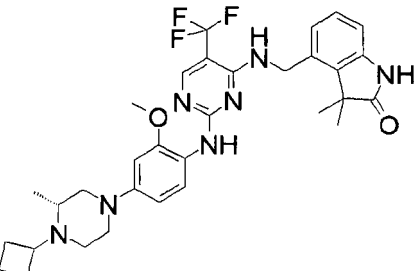
#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-94 (G1-34)			1.65	492.0	G
I-95 (G1-35)		G1-3	1.80	592.3	G
I-96 (G1-36)		G1-3	2.01	562.3	G
I-97 (G1-37)		G1-3	1.77	522.2	G
I-98 (G1-38)		G1-3	1.95	550	G

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(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-99 (G1-39)		G1-3	1.85	536	G
I-100 (G1-40)		G1-3	1.94	521.3	G
I-101 (G1-41)		G1-3	1.98	562.3	G
I-102 (G1-42)		G1-4	1.17	481.2	G
I-103 (G1-43)		C1-6	1.94	549.3/ 551.2	G
I-104 (G2-41)		G2-5	1.86	556.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-105 (G2-42)		G2-8	2.09	640.3	G
I-106 (G2-43)		G2-8	2.14	598.3	G
I-107 (G2-44)		G2-8	2.01	584.3	G
I-108 (G2-45)		G2-8	1.92	570.3	G
I-109 (G2-46)		G2-8	2.15	610.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-110 (G2-47)		G2-1	1.66	639.3	G
I-111 (G2-48)		G2-1	1.95	639.3	G
I-112 (G2-49)		G2-1	1.91	637.3	G
I-113 (G2-50)		G2-1	1.74	636.3	G
I-114 (G2-51)		G2-1	1.86	625.3	G

85

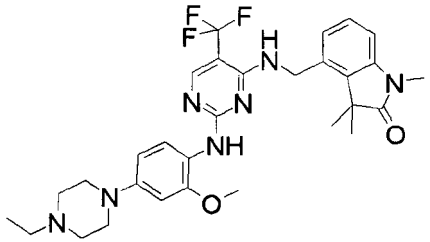
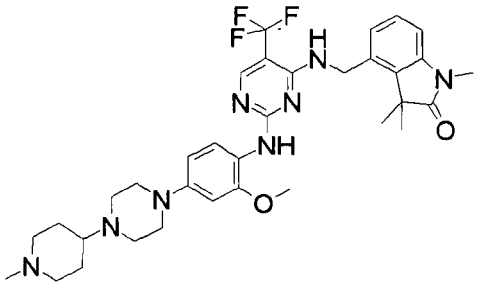
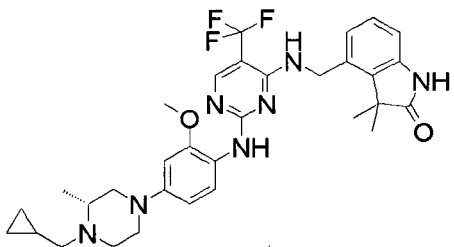
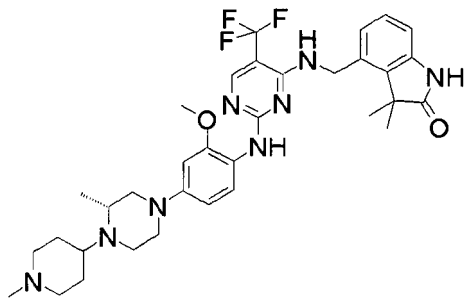
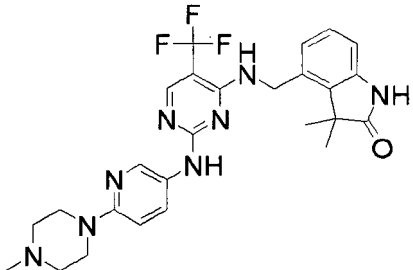
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-120 (G2-57)		G2-1	1.80	605.3	G
I-121 (G2-58)		G2-1	1.69	641.3	G
I-122 (G2-59)		G2-1	1.82	655.3	G
I-123 (G2-60)		G2-1	1.57	668.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-124 (G2-61)		G2-1	1.66	704.3	G
I-125 (G2-62)		G2-1	1.55	675.3	G
I-126 (G2-63)		G2-4	2.00	640.3	G
I-127 (G2-64)		G2-4	1.97	570	G
I-128 (G2-65)		G2-4	2.16	598.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-129 (G2-66)		G2-4	2.06	584.3	G
I-130 (G2-67)		G2-4	2.07	653.3	G
I-131 (G2-68)		G2-8	1.97	610.5	G
I-132 (G2-69)		G2-8	1.82	653.3	G
I-133 (G2-70)			1.43	527	I



(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-134 (G2-71)		G2-9	3.09	553	H
I-135 (G2-72)		G2-5	2.00	639.3	G
I-136 (G2-73)		G2-5	2.03	584.3	G
I-137 (G2-74)		G2-2	2.17	584.3	G
I-138 (G2-75)		G2-6	1.82	542.3	G

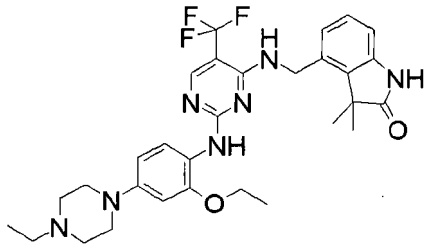
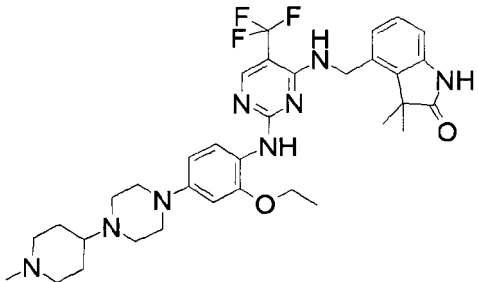
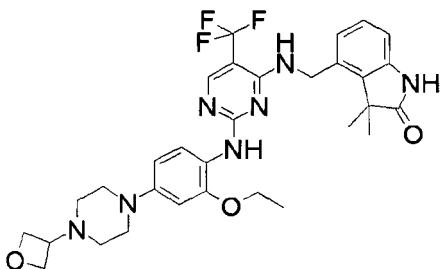
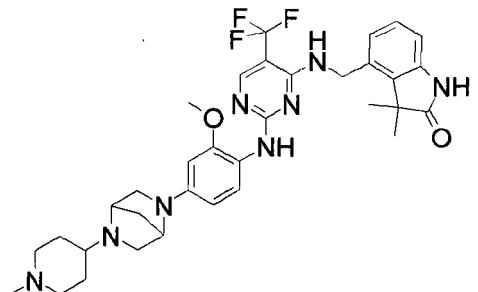
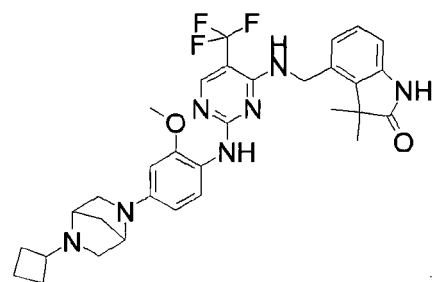
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(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-139 (G2-76)		G2-6	2.00	570.3	G
I-140 (G2-77)		G2-6	1.91	556.3	G
I-141 (G2-78)		G2-6	1.76	584.3	G
I-142 (G2-79)		G2-7	1.96	570.3	G
I-143 (G2-80)		G2-7	2.13	598.3	G

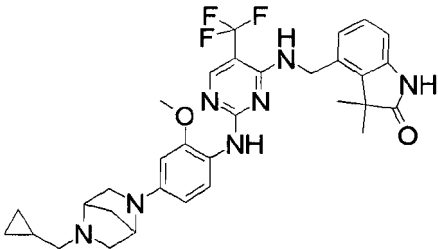
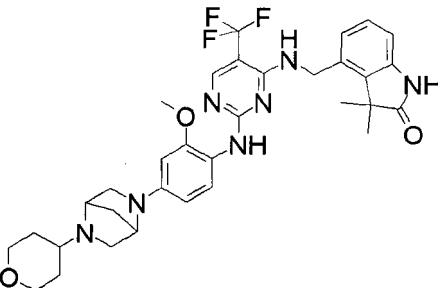
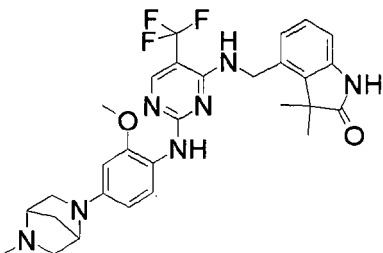
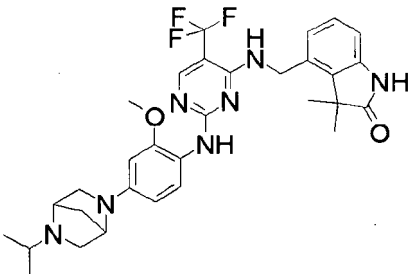
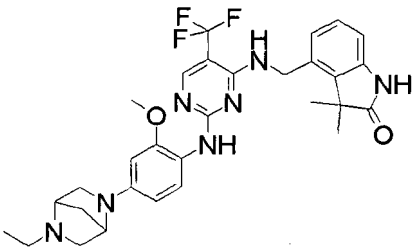
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(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-144 (G2-81)		G2-7	2.04	584.3	G
I-145 (G2-82)		G2-7	2.06	653.3	G
I-146 (G2-83)		G2-7	1.90	612.3	G
I-147 (G2-84)		G2-3	1.95	651.3	G
I-148 (G2-85)		G2-3	2.05	608.3	G

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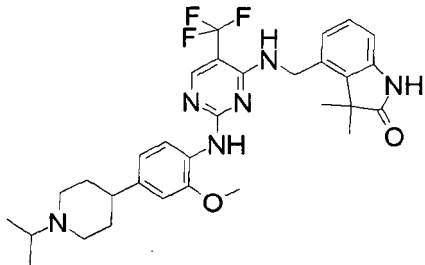
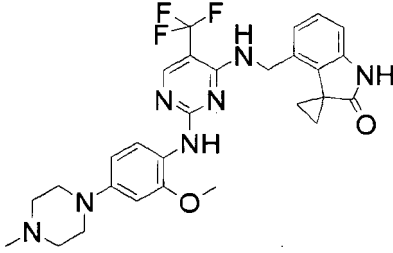
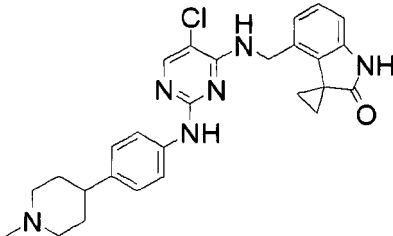
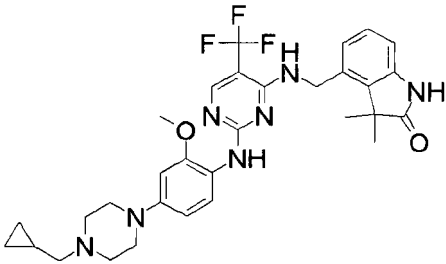
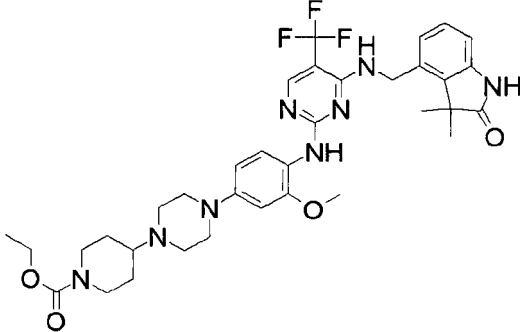
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-149 (G2-86)		G2-3	2.04	608.3	G
I-150 (G2-87)		G2-3	1.86	638.3	G
I-151 (G2-88)		G2-3	1.86	568.3	G
I-152 (G2-89)		G2-3	1.99	596.3	G
I-153 (G2-90)		G2-3	1.94	582.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-154 (G2-91)		G2-3	1.80	610	G
I-155 (G2-92)		G2-5	2.09	596.3	G
I-156 (G2-93)		G2-5	1.81	598	G
I-157 (G2-94)		G2-5	1.95	570.3	G
I-158 (G2-95)		G2-5	1.82	667.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-159 (G2-96)		G2-17	2.29	583.3	G
I-160 (G2-97)			1.78	554.2	G
I-161 (G2-98)			1.79	489.3	G
I-162 (G2-99)		G2-5	2.08	596.3	G
I-163 (G2-100)		G2-5	2.06	697.2	G

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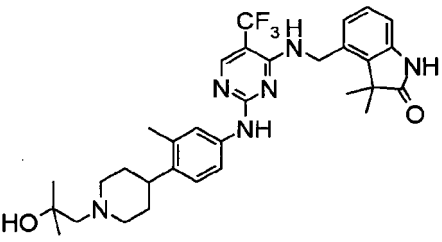
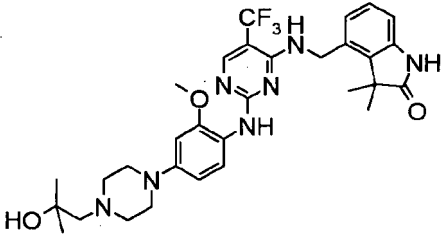
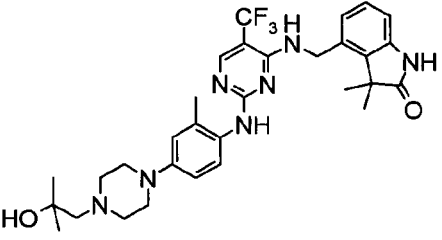
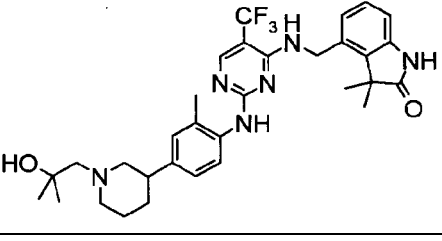
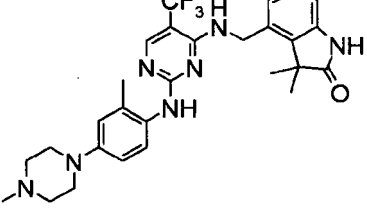
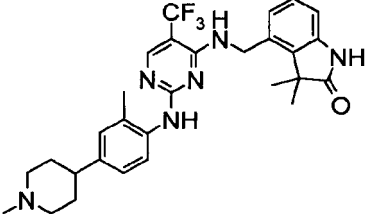
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#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-164 (G2-101)		G2-5	2.07	622.2	G
I-165 (G2-102)		G2-1	1.94	568.2	G
I-166 (G2-103)		G2-1	1.92	669.2	G
I-301 <sup>20</sup> (G2-171)		G2-156	1.58	613	P
I-302 (G2-172)		G2-17	1.38	613	M

(continued)

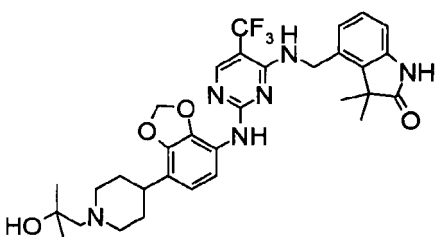
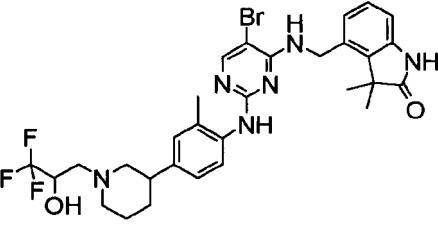
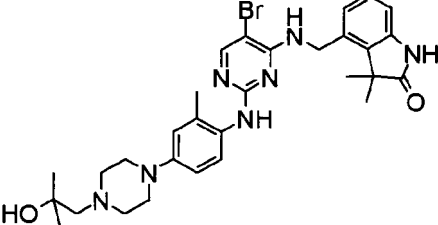
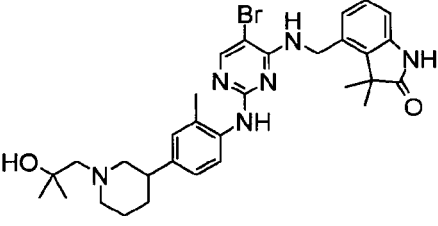
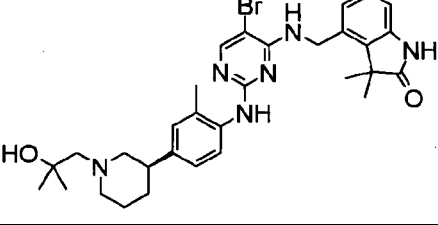
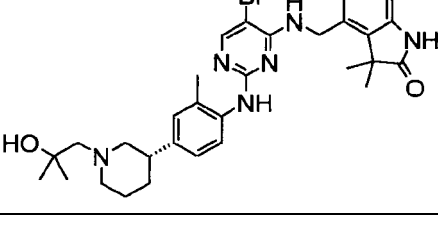
#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-303 (G2-173)		G2-157	1.53	597	M
I-304 (G2-174)		G2-5	1.45	614	P
I-305 (G2-175)		G2-158	1.42	598	P
I-306 <sup>20</sup> (G2-176)		G2-160	1.52	597	M
I-307 (G2-177)		G2-158	1.36	540	P
I-308 (G2-178)		G2-159	1.46	539	P



(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-309 (G2-179)		G2-159	1.36	597	M
I-310 (G2-180)		G2-161	1.41	649	M
I-311 (G2-181)		G2-162	1.40	615	M
I-312 (G2-182)		G2-163	1.39	611	M
I-313 (G2-183)		G2-164	1.33	611	M
I-314 (G2-184)		G2-165	1.42	611	M

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-315 (G2-185)		G2-166	1.33	627	P
I-316 <sup>20</sup> (G1-73)		C1-7	1.51	647/649	P
I-317 (G1-74)		C1-10	1.38	608/610	P
I-318 <sup>20</sup> (G1-75)		C1-7	2.07	607/609	M
I-319 (G1-76)		C1-7	1.51 (4.16)	607/609	M (Q)
I-320 (G1-77)		C1-7	1.51 (5.02)	607/609	M (Q)

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-321 (G1-78)		C1-11	1.41	624/626	P
I-322 <sup>20</sup> (G1-79)		C1-12	1.54	623/625	P
I-323 (G1-80)		C1-13	2.14	623/625	M
I-324 (G1-81)		C1-14	1.91	607/609	M
I-325 <sup>20</sup> (G1-82)		C1-9	1.47	633/635	P
I-326 (G1-83)		C1-5	1.50	603/605	P

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-327 <sup>20</sup> (G1-84)		C1-17	1.38	579/581	M
I-328 <sup>20</sup> (G1-85)		C1-18	1.49	563/565	P
I-329 <sup>20</sup> (G1-86)		C1-18	1.58	603/605	P
I-330 (G1-87)		C1-20	1.27	506/508	P
I-331 (G1-88)		C1-19	1.54	579/581	M
I-332 (G1-89)		C1-5	1.42	505/507	A

(continued)

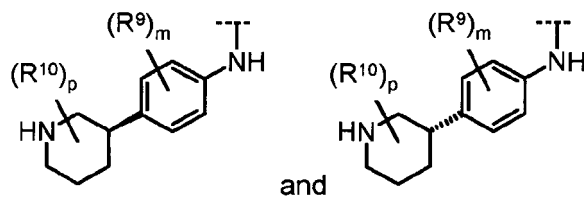
#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-333 <sup>20</sup> (G1-90)		C1-23	1.44	589/591	P
I-334 (G1-91)		C1-21	1.31	563/565	M
I-335 (G1-92)		G1-3	1.4	580/582	P
I-336 (G1-93)		C1-20	1.37	564/566	P
I-337 (G1-94)		C1-26	1.36	581/583	M
I-338 (G1-95)		C1-27	1.35	577/579	M

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-339 (G1-96)		C1-28	1.33	577/579	M
I-340 (G1-97)		C1-29	1.46	633/635	M
I-341 (G1-98)		C1-30	1.27	593/595	M
I-342 (G1-99)		C1-31	1.37	615/617	M
I-343 (G2-186)		G2-167	1.4	615	M
I-344 <sup>20</sup> (G2-187)		G2-168	1.39	611	M

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-345 <sup>20</sup> (G2-188)		G2-169	1.40	615	M
I-346 <sup>20</sup> (G2-189)		G2-170			
I-347 <sup>20</sup> (G1-100)			1.34	577/579	M
I-348 <sup>20</sup> (G1-101)			1.36	581/583	M
I-349 <sup>20</sup> (G1-102)			1.31	593/595	M
<sup>20</sup> racemic representation of the structural formula always explicitly includes both configurations, <i>i.e.</i>					

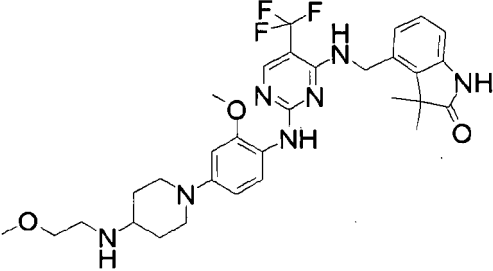
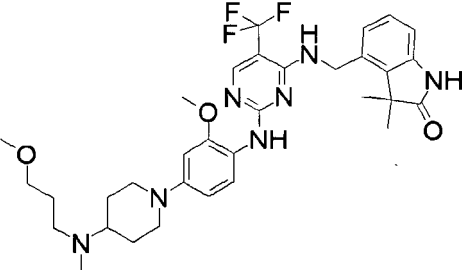
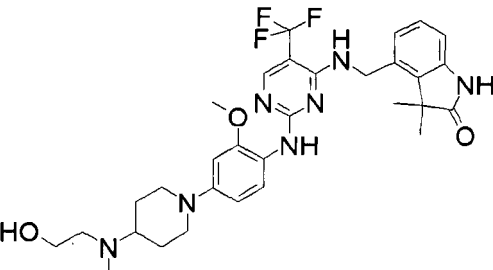
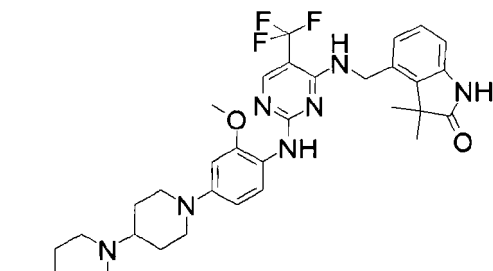


## 4.2.2 General synthesis: Reductive amination on carbonyl compounds G1 or G2 (cf. method Y)

[0234] Reductive amination using G1 or G2 with a carbonyl substructure and amines is carried out according to method Y.

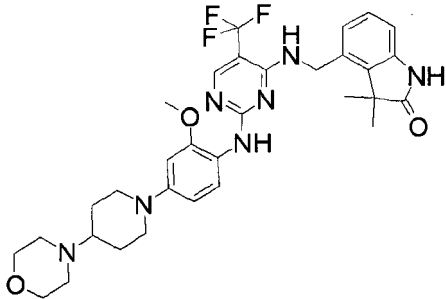
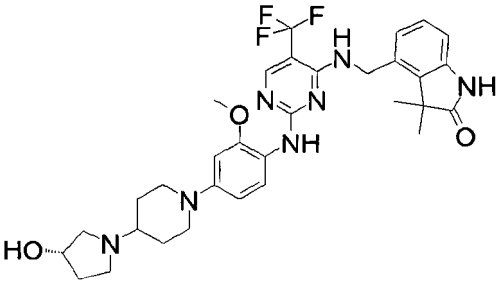
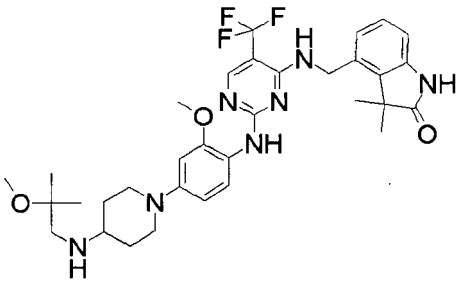
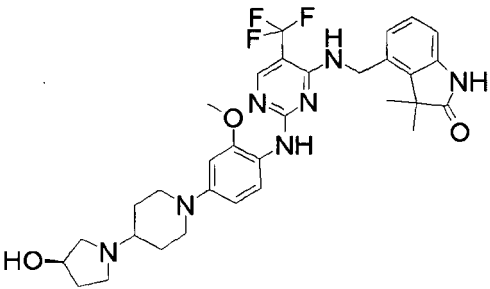
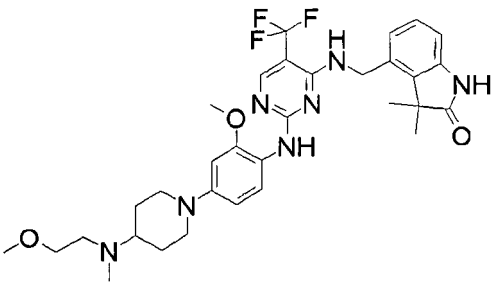
[0235] The following example compounds (Table 24) are obtained by reductive amination of corresponding precursors. The example compounds obtained first may optionally be deprotected by conventional methods and/or be reacted by further standard reactions (e.g. direct alkylation, reductive alkylation, carboxylic acid amide formation, sulphonamide formation, acylation etc.) to obtain further example compounds.

Table 24

#	Structure	educt	$t_{\text{ret}}$ [min]	[M+H] <sup>+</sup>	method of analysis
I-167 (G2-104)		G2-11	1.9	614.3	G
I-168 (G2-105)		G2-11	2.04	642.3	G
I-169 (G2-106)		G2-11	1.84	614	G
I-170 (G2-107)		G2-11	2.02	654.3	G



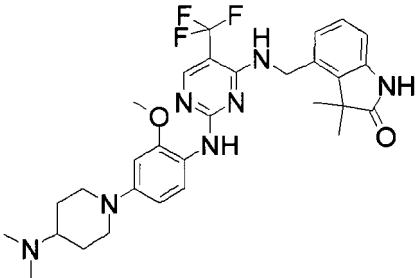
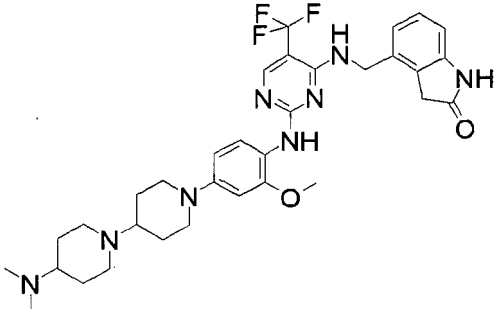
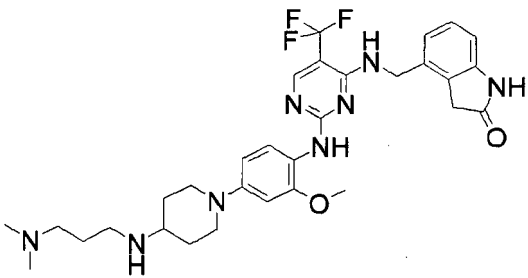
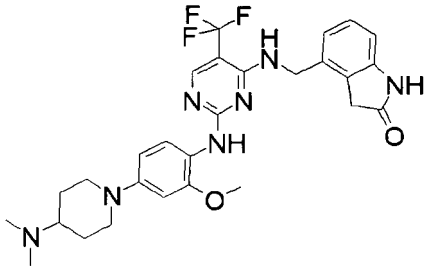
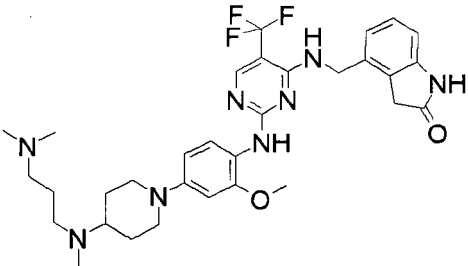
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-171 (G2-108)		G2-11	1.90	626.3	G
I-172 (G2-109)		G2-11	1.83	626.3	G
I-173 (G2-110)		G2-11	2.07	642.3	G
I-174 (G2-111)		G2-11	1.84	626.3	G
I-175 (G2-112)		G2-11	1.98	628.3	G

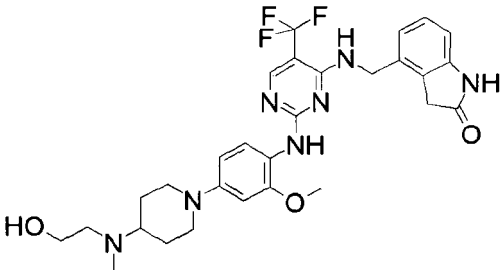
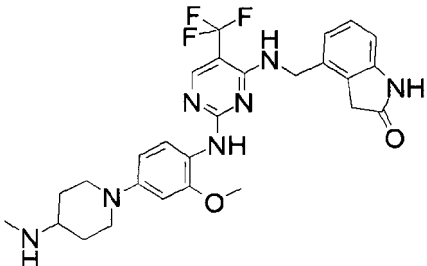
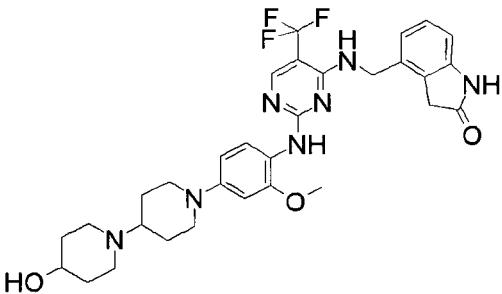
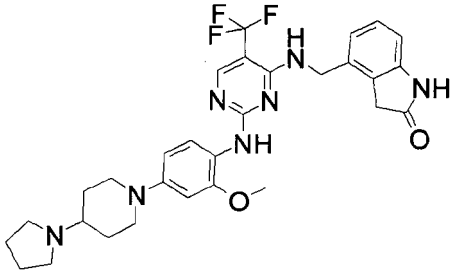
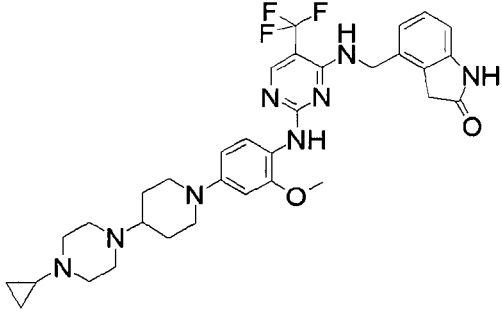
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-176 (G2-113)		G2-11	2.04	596	G
I-177 (G2-114)		G2-11	1.84	640.3	G
I-178 (G2-115)		G2-10	1.92	613.3	G
I-179 (G2-116)		G2-10	1.78	586.3	G
I-180 (G2-117)		G2-11	2.14	610.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-181 (G2-118)		G2-11	2.00	584.3	G
I-182 (G2-119)		G2-10	2.00	639.3	G
I-183 (G2-120)		G2-10	2.09	613.3	G
I-184 (G2-121)		G2-10	1.88	556.3	G
I-185 (G2-122)		G2-10	2.09	627.3	G

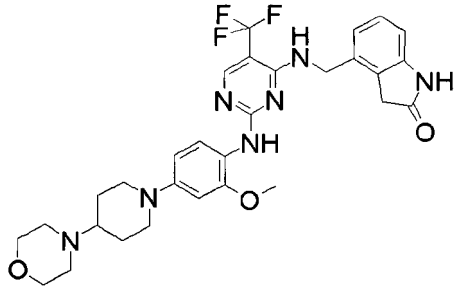
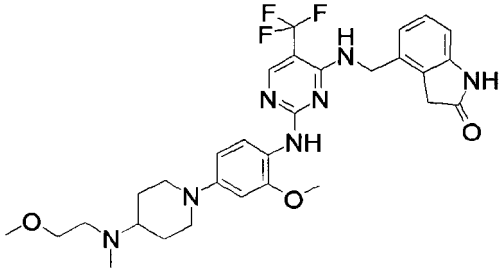
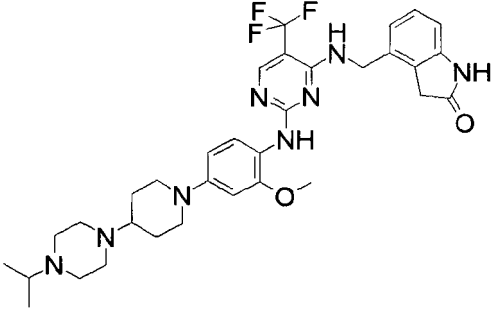
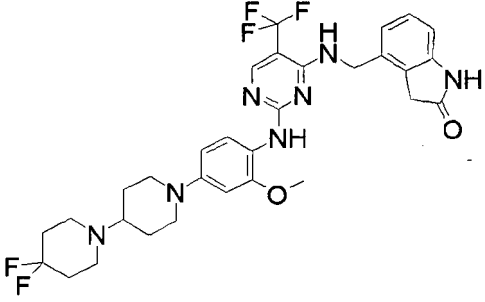
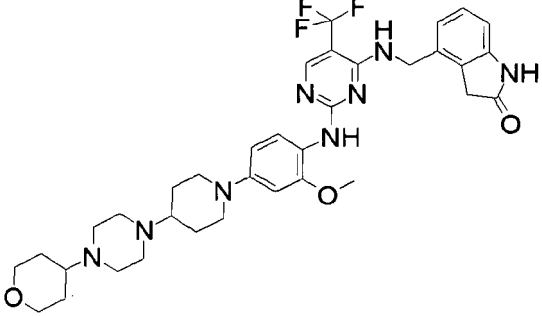
(continued)

#	Structure	educt	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
I-186 (G2-123)		G2-10	1.72	586.3	G
I-187 (G2-124)		G2-10	1.89	542.3	G
I-188 (G2-125)		G2-10	1.72	612.3	G
I-189 (G2-126)		G2-10	2.03	582.3	G
I-190 (G2-127)		G2-10	1.92	637.5	G

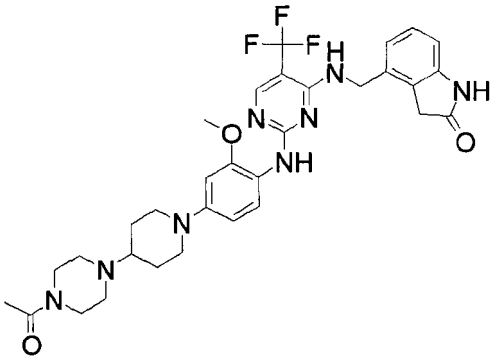
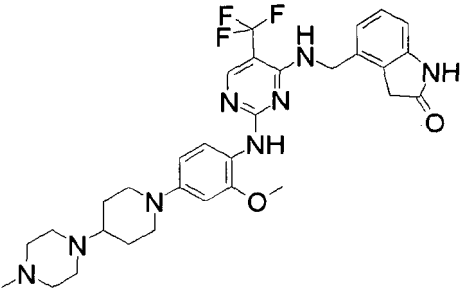
(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-191 (G2-128)		G2-10	1.66	572.3	G
I-192 (G2-129)		G2-10	1.89	626.3	G
I-193 (G2-130)		G2-10	1.83	694.3	G
I-194 (G2-131)		G2-10	1.86	599.3	G
I-195 (G2-132)		G2-10	1.84	621.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-196 (G2-133)		G2-10	1.76	598.3	G
I-197 (G2-134)		G2-10	1.85	600.3	G
I-198 (G2-135)		G2-10	1.88	639.3	G
I-199 (G2-136)		G2-10	2.00	632.3	G
I-200 (G2-137)		G2-10	1.74	681.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-201 (G2-138)		G2-10	1.69	639.3	G
I-202 (G2-139)		G2-10	1.73	611.3	G

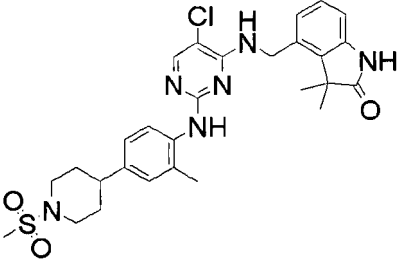
### 4.3 Sulphonylation

#### 4.3.1 General synthesis: sulphonylation (method Z)

[0236] The corresponding compound C1, C2, G1 or G2 is taken up in anhydrous DCM, combined with the sulphonic acid chloride (1.4 equivalents) and triethylamine (3 equivalents) and stirred for 3 h at rt. The reaction mixture is evaporated down, the residue is taken up in DMSO and purified by preparative HPLC-MS. The fractions containing the reaction product are freeze-dried.

[0237] The following Example compounds (Table 25) are obtained by sulphonylation of corresponding precursors. The Example compounds obtained first may optionally be deprotected by conventional methods and/or reacted by further standard reactions (e.g. direct alkylation, reductive alkylation, carboxylic acid amide formation, sulphonamide formation, acylation etc.) to form further Example compounds.

Table 25

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-203 (G1-44)		C1-5	1.38	569.3	G

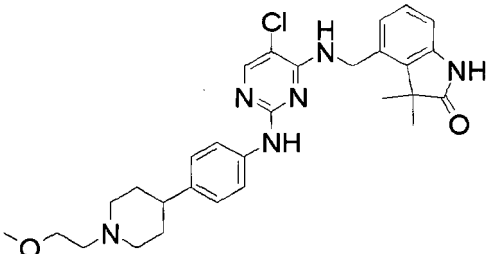
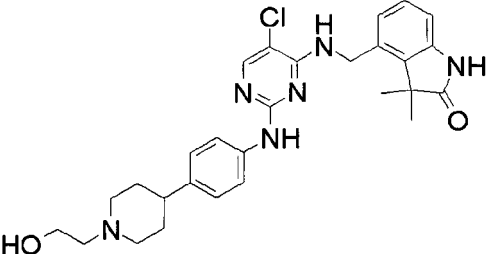
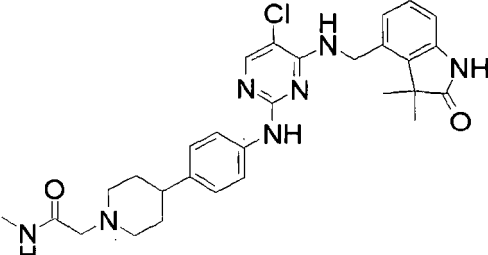
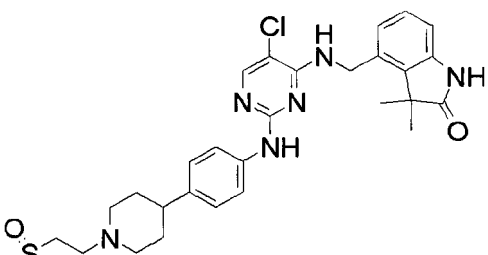
## 4.4 Direct alkylation

## 4.4.1 General synthesis: alkylation (method AA)

**[0238]** The corresponding compound C1, C2, G1 or G2 is taken up in anhydrous DMSO, combined with the alkylhalide (1.2 equivalents) and triethylamine (3 equivalents) and stirred for 12 h at rt. The reaction mixture is purified by preparative HPLC-MS. The fractions containing the reaction product are freeze-dried.

**[0239]** The following Example compounds (Table 26) are obtained by direct alkylation of corresponding precursors. The Example compounds obtained first may optionally be deprotected by conventional methods and/or reacted by further standard reactions (e.g. direct alkylation, reductive alkylation, carboxylic acid amide formation, sulphonamide formation, acylation etc.) to form further Example compounds.

Table 26

#	Structure	educt	$t_{\text{ret}}$ [min]	[M+H] <sup>+</sup>	method of analysis
I-204 (G1-45)		G1-1	4.91	535	J
I-205 (G1-46)		G1-1	2.57	522	H
I-206 (G1-47)		G1-1	2.58	548	I
I-207 (G1-48)		G1-1	2.65	583	I



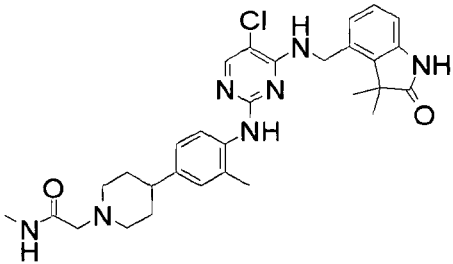
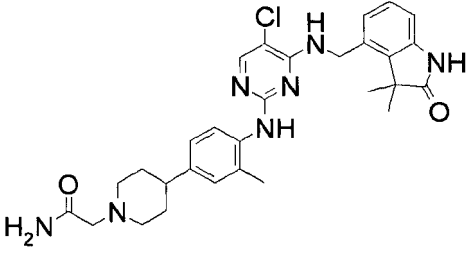
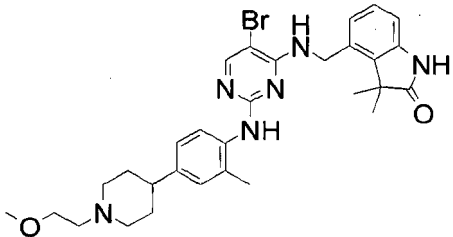
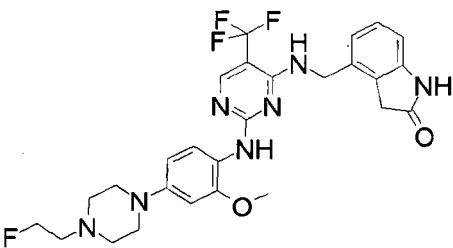
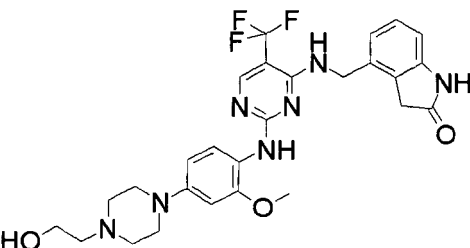
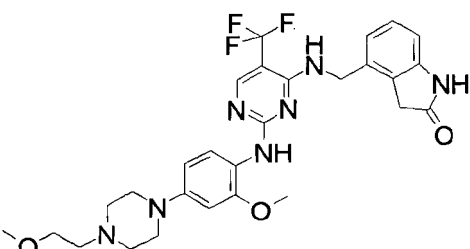
(continued)

#	Structure	educt	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
I-208 (G1-49)		G1-2	2.73	579	H
I-209 (G1-50)		G1-2	2.63	565	H
I-210 (G1-51)		G1-2	2.73	593	J
I-211 (G1-52)		G1-1	2.63	549	H
I-212 (G1-53)		G1-2	2.71	581	H
I-213 (G1-54)		G1-1	2.65	537	H

(continued)

#	Structure	educt	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
I-214 (G1-55)		C1-6	1.82	579.2/581.3	G
I-215 (G1-56)		G1-4	1.19	525.3	G
I-216 (G1-57)		C1-5	1.35	597.3	G
I-217 (G1-58)		C1-5	1.35	535.2	G
I-218 (G1-59)		C1-5	1.36	549.3	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-219 (G1-60)		C1-5	1.36	562.3	G
1-220 (G1-61)		C1-5	1.31	548.3	G
I-221 (G1-62)		C1-6	2.00	593.2/595.2	G
I-222 (G2-140)		G2-1	1.77	560.3	G
I-223 (G2-141)		G2-1	1.61	558.3	G
I-224 (G2-142)		G2-1	1.75	572.3	G

(continued)

#	Structure	educt	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
I-350 <sup>21</sup> (G2-190)		G2-156	1.49	599	P
I-351 <sup>21</sup> (G2-191)		G2-156	1.39	585	P
I-352 (G2-192)		G2-159	1.46	583	P
I-353 (G2-193)		G2-5	1.39	600	P
I-354 <sup>21</sup> (G2-194)		G2-160	1.40	569	P
I-355 (G2-195)		G2-159	1.38	569	P

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-356 <sup>21</sup> (G2-196)		G2-160	1.48	583	P
I-357 <sup>21</sup> (G1-103)		C1-9	1.39	579/581	P
I-358 <sup>21</sup> (G1-104)		C1-9	1.29	565/567	P
I-359 <sup>21</sup> (G1-105)		C1-7	1.47	593/595	P
I-360 <sup>21</sup> (G1-106)		C1-12	1.47	609/611	P

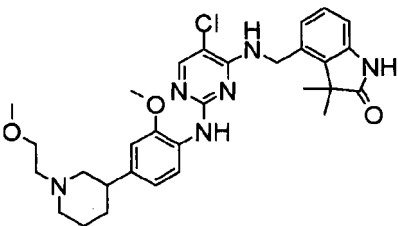
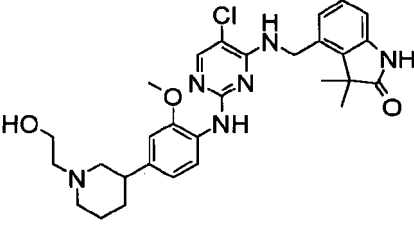
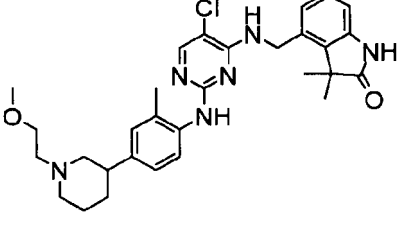
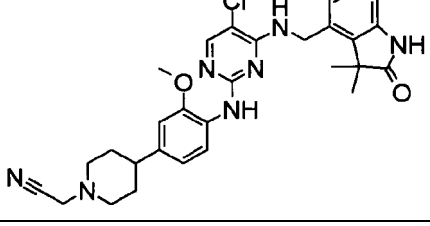
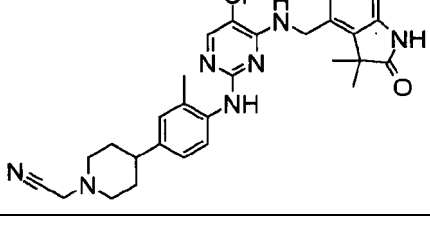
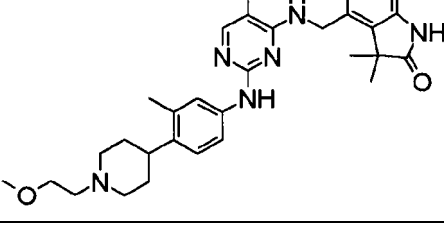
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#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-361 <sup>21</sup> (G1-107)		C1-12	1.37	595/597	P
I-362 (G1-108)		C1-7	1.63 (7.54)	593/595	P (R)
I-363 (G1-109)		C1-7	1.63 (8.69)	593/595	P (R)
I-364 <sup>21</sup> (G1-110)		C1-7	1.62	579/581	P
I-365 <sup>21</sup> (G1-111)		C1-9	1.32	592/594	P

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-366 <sup>21</sup> (G1-112)		C1-7	1.36	606/608	P
I-367 (G1-113)		C1-15	1.5	607/609	P
I-368 <sup>21</sup> (G1-114)		C1-16	1.49	607/609	P
I-369 (G1-115)		C1-11	1.37	610/612	P
I-370 (G1-116)		C1-5	1.36	562/564	P

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-371 <sup>21</sup> (G1-117)		C1-17	1.45	565/567	P
I-372 <sup>21</sup> (G1-118)		C1-17	1.34	551/553	P
I-373 <sup>21</sup> (G1-119)		C1-18	1.41	549/551	P
I-374 (G1-120)		C1-19	1.41	546/548	P
I-375 (G1-121)		C1-5	1.38	530/532	P
I-376 (G1-122)		C1-21	1.98	549/551	M

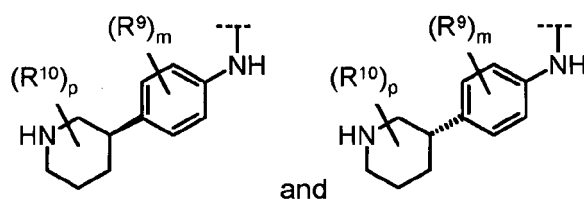


(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-377 (G1-123)		C1-5	1.32	563/565	M
I-378 (G1-124)		C1-22	1.38	577/579	M
I-379 <sup>21</sup> (G1-125)		C1-23	1.30	548/550	P
I-380 <sup>21</sup> (G1-126)		C1-23	1.44	535/537	P
I-381 <sup>21</sup> (G1-127)		C1-23	1.25	521/523	P
I-382 <sup>21</sup> (G1-128)		C1-18	1.32	535/537	P

(continued)

#	Structure	educt	$t_{\text{ret}}$ [min]	$[M+H]^+$	method of analysis
I-383 <sup>21</sup> (G1-129)		C1-18	1.32	562/564	P
I-384 <sup>21</sup> (G1-130)		C1-24	1.46	563/565	P
I-385 (G1-131)		C1-22	1.47	563/565	P
I-386 (G1-132)		C1-25	1.34	566/568	P
<sup>21</sup> racemic representation of the structural formula always explicitly includes both configurations, <i>i.e.</i>					



#### 4.5 Amide coupling to carboxylic acid components G1 or G2 (cf. method X)

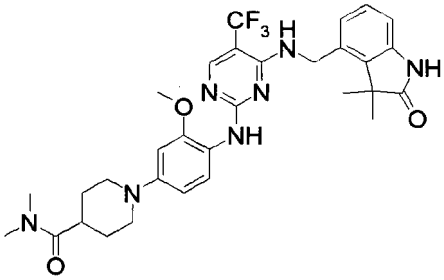
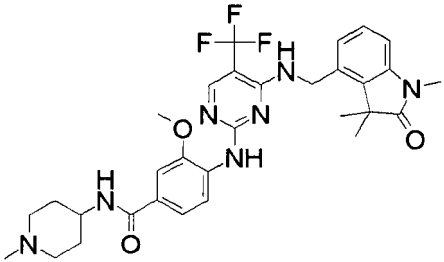
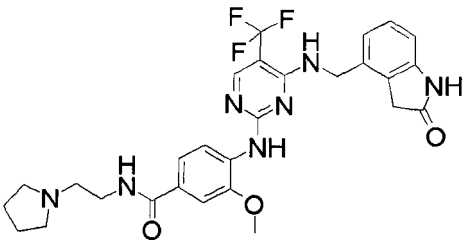
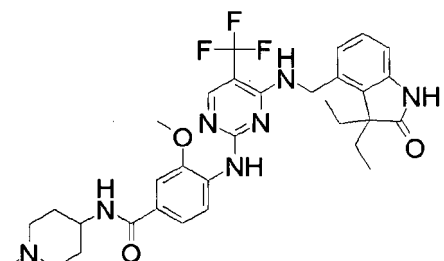
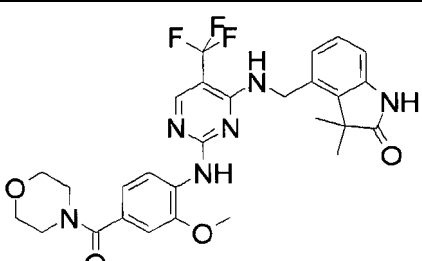
**[0240]** The amide coupling is carried out analogously to method X (*i.e.* with TBTU), except that in this case the corresponding compound **G1** or **G2** has the carboxyl function and is reacted with an amine.

**[0241]** The following Example compounds (Table 27) are obtained by amide coupling of corresponding precursors. The Example compounds obtained first may optionally be deprotected by conventional methods and/or reacted by further standard reactions (e.g. direct alkylation, reductive alkylation, carboxylic acid amide formation, sulphonamide formation, acylation etc.) to form further Example compounds.

Table 27

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-225 (G2-143)		G2-14	1.97	612.3	G
I-226 (G2-144)		G2-12	1.75	681.5	G
I-227 (G2-145)		G2-12	1.58	598.5	G
I-228 (G2-146)		G2-14	1.77	598.3	G
I-229 (G2-147)			1.82	584.2	G

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-230 (G2-148)		G2-12	1.70	612.5	G
I-231 (G2-149)			1.90	612.3	G
I-232 (G2-150)			1.80	570.3	G
I-233 (G2-151)			1.91	626.2	G
I-234 (G2-152)		G2-14	3.86	571	H

(continued)

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-235 (G2-153)			1.19	525.3	G

#### 4.6 Derivatisation on phenolic components G1 or G2 (method AB)

[0242] The corresponding compound **G1** or **G2**, an organic halide (e.g. alkylhalide, 0.9 equivalents) and potassium carbonate (1.9 equivalents) are stirred in DMF for 48 h at 100 °C. The reaction mixture is divided between DCM and saturated saline solution and the aqueous phase is exhaustively extracted. The organic phase is dried on sodium sulphate, filtered and evaporated down. The crude product is purified by preparative HPLC. The fractions containing the reaction product are freeze-dried.

[0243] Alternatively derivatisation may also be carried out on the phenolic hydroxyl function by MITSONOBU reaction.

[0244] The following Example compounds (Table 28) are obtained by alkylation of corresponding precursors. The Example compounds obtained first may optionally be deprotected by conventional methods and/or reacted by further standard reactions (e.g. direct alkylation, reductive alkylation, carboxylic acid amide formation, sulphonamide formation, acylation etc.) to form further Example compounds.

Table 28

#	Structure	educt	t <sub>ret</sub> [min]	[M+H] <sup>+</sup>	method of analysis
I-236 (G2-154)		G2-13	1.97	612.3	G
I-237 <sup>22</sup> (G2-155)		G2-10	1.63	529.3	G
<sup>22</sup> synthesis by reduction of <b>G2-10</b>					

[0245] The following Examples describe the biological activity of the compounds according to the invention, without restricting the invention to these Examples.

[0246] Compounds of general formula (I) are characterised by their many possible applications in the therapeutic field. Particular mention should be made of those applications in which the inhibiting effect on the proliferation of cultivated human tumour cells but also on the proliferation of other cells such as endothelial cells, for example, are involved.

*Insulin-like Growth Factor-1 Receptor (IGF-1R)-Kinase Assay*

**[0247]** The kinase activity is measured by DELFIA® assay (dissociation-enhanced lanthanide fluorescence immunoassay, Perkin Elmer). The cytoplasmic kinase domain of human IGF-1R (amino acids 964 - 1370) is expressed as a fusion protein with a glutathione-S-transferase tag (IGF-1R-GST) in High Five™ Cells (Invitrogen). Enzyme activity is measured in the presence of substances and a control substance. Poly-glutamate-tyrosine peptide (pEY, Sigma Aldrich) and biotinylated pEY (bio-pEY) are used as reaction substrates.

**[0248]** 10 µL of substance in 25 % DMSO are mixed with 30 µL of IGF-1 R-GST solution (67 mM HEPES pH 7.4, 15 µg/mL pEY, 1.7 µg/mL bio-pEY, 13.3 mM MgCl<sub>2</sub>, 3.3 mM dithiothreitol, 0.0033 % Brij 35, 2 ng IGF-1 R-GST) in 96-well plates. The reactions are started with 10 µL of a 750 µM ATP solution. After 40 min at RT the reactions are stopped with 50 µL of stop solution (250 mM EDTA, 20 mM HEPES pH 7.4). 90 µL from each reaction are transferred onto streptavidin-coated 96-well plates. After 120 min incubation at rt the plates are washed three times with 200 µL phosphate-buffered saline (PBS) per well. The plates are incubated for 60 min with 100 µL of europium-coupled antibody against phospho-tyrosine (diluted 1/2000 in Perkin Elmer DELFIA assay buffer) per well. The plates are washed three times with 200 µL per well of DELFIA washing buffer. 100 µL DELFIA Enhancement Solution (Perkin Elmer) is added to each well, and the plates are incubated for 10 min. The fluorescence signal is measured with a Wallac Victor TRF Reader. IC<sub>50</sub> values for the inhibition of the IGF-1 R-kinase activity are calculated using the programmes Fifty (Version 2) and GraphPad (Version 3.0).

**[0249]** Table 29 shows the IC<sub>50</sub> values of the example compounds determined using the above assay.

**Table 29**

#	IGF1R IC <sub>50</sub> [nM]	#	IGF1R IC <sub>50</sub> [nM]	#	IGF1R IC <sub>50</sub> [nM]
I-2	21	I-48	7	I-65	2
I-7	0.69	I-49	5	I-66	6
I-8	28	I-50	3	I-67	15
I-11	2	I-51	2	I-68	0.4
I-25	7	I-52	7	I-69	1
I-26	9	I-53	6	I-70	21
I-30	3	I-54	7	I-71	50
I-31	0.7	I-55	1	I-72	72
I-32	3	I-56	2	I-73	29
I-33	0.6	I-57	0.76	I-74	2
I-41	0.2	I-58	1	I-75	2
I-42	0.79	I-59	4	I-76	11
I-43	7	I-60	3	I-77	3
I-44	25	I-61	3	I-78	30
I-45	23	I-62	1	I-79	4
I-46	29	I-63	2	I-80	47
I-47	38	I-64	2	I-81	81

#	IGF1R IC <sub>50</sub> [nM]
I-82	65
I-83	5
I-84	0.3
I-85	9
I-86	1
I-87	3
I-88	9
I-89	0.18
I-90	0.32
I-91	6
I-92	9
I-93	5
I-94	14
I-95	16
I-96	3
I-97	2
I-98	2
I-99	2
I-100	2
I-101	2
I-102	4
I-103	0.69
I-104	0.1
I-105	2
I-106	0.08
I-107	0.62
I-108	0.93
I-109	0.87
I-110	8
I-111	18
I-112	5

#	IGF1R IC <sub>50</sub> [nM]
I-113	3
I-114	4
I-115	10
I-116	10
I-117	9
I-118	11
I-119	11
I-120	49
I-121	16
I-122	15
I-123	12
I-124	12
I-125	15
I-126	3
I-127	3
I-128	2
I-129	2
I-130	2
I-131	0.33
I-132	0.6
I-133	13
I-134	1
I-135	0.57
I-136	2
I-137	65
I-138	13
I-139	8
I-140	11
I-141	19
I-142	0.55
I-143	1

#	IGF1R IC <sub>50</sub> [nM]
I-144	0.81
I-145	0.67
I-146	4
I-147	5
I-148	3
I-149	2
I-150	3
I-151	2
I-152	3
I-153	2
I-154	13
I-155	1
I-156	4
I-157	0.61
I-158	2
I-159	0.41
I-160	4
I-161	0.96
I-162	2
I-163	10
I-164	14
I-165	4
I-166	11
I-167	0.2
I-168	0.2
I-169	0.26
I-170	0.33
I-171	0.38
I-172	0.4
I-173	0.46
I-174	0.81

#	IGF1R IC <sub>50</sub> [nM]
I-175	0.87
I-176	0.98
I-177	1
I-178	2
I-179	2
I-180	2
I-181	2
I-182	3
I-183	3
I-184	4
I-185	4
I-186	4
I-187	4
I-188	5
I-189	5
I-190	6
I-191	6
I-192	6
I-193	7
I-194	7
I-195	7
I-196	8

#	IGF1R IC <sub>50</sub> [nM]
I-197	9
I-198	11
I-199	11
I-200	13
I-201	20
I-202	24
I-203	14
I-204	2
I-205	2
I-206	5
I-207	10
I-208	0.68
I-209	1
I-210	0.47
I-211	3
I-212	3
I-213	4
I-214	0.62
I-215	12
I-216	2
I-217	1
I-218	1

#	IGF1R IC <sub>50</sub> [nM]
I-219	2
I-220	2
I-221	0.98
I-222	32
I-223	18
I-224	18
I-225	2
I-226	2
I-227	5
I-228	8
I-229	12
I-230	13
I-231	15
I-232	47
I-233	58
I-234	8
I-235	14
I-236	0.51
I-237	21
I-238	1.0
I-254	2.2

#	IGF1R IC <sub>50</sub> [nM]
I-291	6.0
I-292	5.0
I-293	10.0
I-294	7.0
I-295	4.0
I-296	1.0
I-297	9.0

#	IGF1R IC <sub>50</sub> [nM]
I-298	7.0
I-299	8.0
I-300	11.0
I-301	1.6
I-302	0.6
I-303	0.2
I-304	1.0

#	IGF1R IC <sub>50</sub> [nM]
I-305	2.0
I-306	1.0
I-307	1.0
I-308	0.8
I-309	1.0
I-310	5.0
I-311	15.0



#	IGF1R IC50 [nM]
I-312	27.0
I-313	0.5
I-314	5.0
I-315	1.9
I-316	2.0
I-317	6.0
I-318	0.4
I-319	2.0
I-320	0.9
I-321	2.0
I-322	0.5
I-323	0.9
I-324	0.1
I-325	2.0
I-326	2.0
I-327	1.0
I-328	1.0
I-329	2.0
I-330	3.0
I-331	1.0
I-332	1.0
I-333	2.0
I-334	0.4
I-335	3.0

#	IGF1R IC50 [nM]
I-336	4.0
I-337	9.0
I-339	2.1
I-340	11.0
I-341	0.9
I-342	3.0
I-343	4.0
I-344	1.1
I-345	5.7
I-347	2.8
I-348	8.4
I-350	0.5
I-351	0.5
I-352	0.8
I-353	2.0
I-354	1.0
I-355	0.5
I-356	0.8
I-357	0.7
I-358	0.7
I-359	0.5
I-360	0.6
I-361	0.4
I-362	0.3

#	IGF1R IC50 [nM]
I-363	2.0
I-364	0.6
I-365	1.0
I-366	2.0
I-367	3.0
I-368	2.0
I-369	2.0
I-370	2.0
I-371	0.8
I-372	0.8
I-373	0.4
I-374	11.0
I-375	9.0
I-376	0.6
I-377	0.9
I-378	6.0
I-379	6.0
I-380	2.0
I-381	0.9
I-382	1.0
I-383	2.0
I-384	6.0
I-385	4.0
I-386	3.0

#### Cellular IGF-1R-phosphorylation assay

**[0250]** The activity of substances against the phosphorylation of IGF-1R in activated cells is measured as follows: mouse fibroblast cells (transfected with human IGF-1R, Fibro-hIGF-1R) are cultivated in standard medium (DMEM, 10 % foetal calf serum (FCS, Gibco), 1x MEM Non-Essential Amino Acids (NEAA, Gibco), 7.5 % sodium hydrogen carbonate (Gibco) and 0.3 mg/mL Puromycin (Sigma)) in a humid incubator at 37°C with 5 % CO<sub>2</sub>/95 % air.

**[0251]** 10000 Fibro-hIGF-1R cells per well in 200 µL of standard medium are seeded into 96-well plates and cultivated overnight. The next day, the medium is suction filtered and the cells are cultivated in 90 µL serum-reduced medium (DMEM, 0.5 % FCS, 1x MEM NEAA, 7.5 % sodium hydrogen carbonate) for a further 24 h. 10 µL of substance solution (diluted in serum-reduced medium) is added thereto, and the cells are incubated for a further 120 min in the incubator. The phosphorylation of IGF-1R is activated for 30 min by the addition of IGF-1 (20 ng/mL in serum-reduced medium). All further incubations are carried out at RT. The supernatant is suction filtered from the wells, and the cells are fixed in 100 µL per well of 4 % paraformaldehyde (diluted in PBS). The supernatant in the well is suction filtered and the cells are permeabilised for 5 min in 300 µL per well of 0.1 % TritonX-100 (diluted in PBS). The supernatants are suction filtered once again and the cells are incubated for 20 min in quenching buffer (PBS with 0.1 % TritonX-100 and 1.2 % hydrogen peroxide), to inhibit the endogenous peroxidase of the cells. The cells are washed for 5 min with 300 µL per

well of PBS with 0.1 % TritonX-100 and then incubated for 60 min with 100  $\mu$ L per well of blocking buffer (PBS with 0.1 % TritonX-100 and 5 % Bovine Serum Albumin (BSA)). The blocking buffer is exchanged for 50  $\mu$ L of the first antibody buffer (1/1000 dilute anti-phospho-IGF-1 receptor  $\beta$  (Tyr1135/1136) / insulin receptor  $\beta$  (Tyr1150/1151) (19H7) rabbit monoclonal antibody from Cell Signaling Technology in blocking buffer) and the plates are incubated overnight at 4 °C. The next day the plates are washed for 5 min with 300  $\mu$ L PBS/0.1 % TritonX-100 at RT and then incubated for 60 min with 50  $\mu$ L per well of the second antibody buffer (1/500 diluted Goat Anti-Rabbit Immunoglobulin-Horseradish Peroxidase (HRP) (Dako) in blocking buffer) at RT. The plates are washed first for 5 min with 300  $\mu$ L PBS/0.1 % TritonX-100 and then for a further 5 min with 300  $\mu$ L PBS at rt. The plates are developed for 10 min with 100  $\mu$ L per well of a peroxidase solution (1:1 mixture of TMB Peroxidase Substrate and Peroxidase Solution B from Kirkegaard & Perry Laboratories, Inc.). The reactions are stopped with 100  $\mu$ L per well of stop solution (1M phosphoric acid). The absorbance in each well is measured at 450 nm with a SpectraMax Absorbance Reader. EC<sub>50</sub> values for inhibiting the phosphorylation of the IGF-1R in activated cells are calculated using the programmes Fifty (Version 2) and GraphPad (Version 3.0).

**[0252]** Compounds (I) according to the invention generally display a good inhibitory effect in the cellular assay described above, i.e. for example an EC<sub>50</sub> value of less than 5  $\mu$ mol/L, often less than 3  $\mu$ mol/L.

#### Cell Proliferation Assays

**[0253]** Compounds were tested for their anti-proliferative effects in the TC-71 (Ewing's sarcoma) and HCT 116 (colorectal carcinoma) cancer cell lines in vitro. Published scientific data has described that interference with the Insulin-like Growth Factor-1 Receptor (IGF-1R) signaling pathway reduces the proliferation of TC-71 cells [1]. Therefore TC-71 cells served as a positive control cell line for monitoring the activity of compounds against IGF-1R-mediated cell proliferation. In contrast, published data has demonstrated that the proliferation of HCT 116 cells is independent of IGF-1 R signaling [2]. Therefore the HCT 116 cell line served as a negative control.

**[0254]** 2000 TC-71 cells or 1000 HCT 116 cells were seeded per well in 180  $\mu$ L IMDM + 10 % foetal calf serum (FCS) + penicillin/streptomycin into 96-well microtitre plates. The plates were placed in a cell culture incubator (37°C in a humidified atmosphere of 95 % O<sub>2</sub>/5 % CO<sub>2</sub>) overnight. The following day, serial dilutions of compounds, prepared in duplicates, were transferred onto the cell layers (controls without compound). The cells were cultivated for a further 72 h in the cell culture incubator. 20  $\mu$ L of Alamar Blue™ (Serotec Ltd, Düsseldorf, Germany) was added to each well and the plates incubated for 7 h in the cell culture incubator. Fluorescence (extinction wavelength of 544 nm and emission at 590 nm) was then measured and the normalized data fitted by iterative calculation with a sigmoidal curve analysis program (Graph Pad Prism) with a variable Hill slope to determine the IC<sub>50</sub> values.

**[0255]** The EC<sub>50</sub> ranges of the following compounds were determined on TC-71 cells according to this assay ("+++" < 50 nM; 50 nM < "++" < 250 nM; 250 nM < "+" < 3  $\mu$ M):

#	EC <sub>50</sub> TC-71 [nM]
I-238	++
I-31	+++
I-53	++
I-54	++
I-55	++
I-56	+
I-57	+++
I-66	+
I-67	++
I-68	+++
I-69	+++

#	EC <sub>50</sub> TC-71 [nM]
I-291	++
I-292	++
I-293	++
I-294	+
I-295	++
I-296	++
I-297	++
I-298	++
I-299	+++
I-300	+++
I-97	+++

#	EC <sub>50</sub> TC-71 [nM]
I-102	++
I-103	+++
I-104	+++
I-160	+
I-301	+++
I-302	+++
I-303	+++
I-304	+++
I-305	++
I-306	+++
I-307	+++

5  
10  
15  
20  
25  
30  
35  
40

#	EC <sub>50</sub> TC-71 [nM]
I-308	+++
I-309	+++
I-310	++
I-311	++
I-312	++
I-313	+++
I-314	++
I-316	++
I-317	+++
I-318	+++
I-319	+++
I-320	+++
I-321	+++
I-322	+++
I-323	+++
I-324	+++
I-325	++
I-326	++
I-327	+++
I-328	+++
I-329	+++
I-330	+++
I-331	+++
I-332	+++
I-333	+
I-334	+++
I-335	+++
I-336	++
I-337	+
I-338	+

#	EC <sub>50</sub> TC-71 [nM]
I-339	+++
I-340	++
I-341	+++
I-342	+++
I-203	+
I-204	++
I-208	++
I-209	++
I-210	+++
I-211	++
I-212	++
I-213	++
I-214	+++
I-215	+
I-216	++
I-217	++
I-218	+++
I-219	+++
I-220	++
I-221	+++
I-350	+++
I-351	+++
I-352	+++
I-353	+++
I-354	+++
I-355	+
I-356	+++
I-357	++
I-358	+++
I-359	+++

#	EC <sub>50</sub> TC-71 [nM]
I-360	+++
I-361	+++
I-362	+++
I-363	++
I-364	+++
I-365	++
I-366	++
I-367	+++
I-368	+++
I-369	+++
I-370	+++
I-371	+++
I-372	+++
I-373	++
I-374	++
I-375	+++
I-376	+++
I-377	+++
I-378	++
I-379	++
I-380	++
I-381	++
I-382	+++
I-383	++
I-384	++
I-385	++
I-386	+++
I-235	+

[0256] In addition to TC-71, several other cancer cell lines from diverse tissue origins, which have previously been demonstrated to be sensitive to IGF-1R inhibition, were shown to be sensitive to compounds (I). Examples include COLO 205 (colorectal cancer) [3], LP-1 (multiple myeloma) [4] and HL-60 (acute myeloid leukemia) [5].

#### Reference List

#### [0257]

1 Manara, M.C., Landuzzi, L., Nanni, P., Nicoletti, G., Zambelli, D., Lollini, P.L., Nanni, C., Hofmann, F., Garcia-Echeverria, C., Picci, P. and Scotlandi, K. (2007) Preclinical in vivo study of new insulin-like growth factor-I receptor-specific inhibitor in Ewing's sarcoma. Clin. Cancer Res., 13, 1322-1330.

2 Pitts, T.M., Tan, A.C., Kulikowski, G.N., Tentler, J.J., Brown, A.M., Flanigan, S.A., Leong, S., Coldren, C.D., Hirsch, F.R., Varela-Garcia, M., Korch, C. and Eckhardt, S.G. (2010) Development of an integrated genomic classifier for a novel agent in colorectal cancer: approach to individualized therapy in early development. Clin Cancer Res., 16, 3193-3204.

3 Haluska, P., carboni, J.M., Loegering, D.A., Lee, F.Y., Wittman, M., Saulnier, M.G., Frennesson, D.B., Kalli, K.R., Conover, C.A., Attar, R.M., Kaufmann, S.H., Gottardis, M. and Erlichman, C. (2006) In vitro and in vivo antitumor effects of the dual insulin-like growth factor-I/insulin receptor inhibitor, BMS-554417. *Cancer Res.*, 66, 362-371.

4 Georgii-Hemming, P., Wiklund, H.J., Ljunggren, O. and Nilsson, K. (1996) Insulin-like growth factor I is a growth and survival factor in human multiple myeloma cell lines. *Blood*, 88, 2250-2258.

5 Wahner Hendrickson, A.E., Haluska, P., Schneider, P.A., Loegering, D.A., Peterson, K.L., Attar, R., Smith, B.D., Erlichman, C., Gottardis, M., Karp, J.E., carboni, J.M. and Kaufmann, S.H. (2009) Expression of insulin receptor isoform A and insulin-like growth factor-1 receptor in human acute myelogenous leukemia: effect of the dual-receptor inhibitor BMS-536924 in vitro. *Cancer Res.*, 69, 7635-7643.

**[0258]** On the basis of their biological properties the compounds of general formula (I) according to the invention, their tautomers, racemates, enantiomers, diastereomers, mixtures thereof and the salts of all the above-mentioned forms are suitable for treating diseases characterised by excessive or abnormal cell proliferation.

**[0259]** Such diseases include for example: viral infections (e.g. HIV and Kaposi's sarcoma); inflammatory and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphomas and solid tumours (e.g. carcinomas and sarcomas), skin diseases (e.g. psoriasis); diseases based on hyperplasia which are characterised by an increase in the number of cells (e.g. fibroblasts, hepatocytes, bones and bone marrow cells, cartilage or smooth muscle cells or epithelial cells (e.g. endometrial hyperplasia)); bone diseases and cardiovascular diseases (e.g. restenosis and hypertrophy). They are also suitable for protecting proliferating cells (e.g. hair, intestinal, blood and progenitor cells) from DNA damage caused by radiation, UV treatment and/or cytostatic treatment.

**[0260]** For example, the following cancers may be treated with compounds according to the invention, without being restricted thereto: brain tumours such as for example acoustic neurinoma, astrocytomas such as pilocytic astrocytomas, fibrillary astrocytoma, protoplasmic astrocytoma, gemistocytary astrocytoma, anaplastic astrocytoma and glioblastoma, brain lymphomas, brain metastases, hypophyseal tumour such as prolactinoma, HGH (human growth hormone) producing tumour and ACTH producing tumour (adrenocorticotrophic hormone), craniopharyngiomas, medulloblastomas, meningiomas and oligodendrogliomas; nerve tumours (neoplasms) such as e.g. tumours of the vegetative nervous system such as neuroblastoma sympathicum, ganglioneuroma, paraganglioma (pheochromocytoma, chromaffinoma) and glomus-caroticum tumour, tumours on the peripheral nervous system such as amputation neuroma, neurofibroma, neurinoma (neurilemmoma, Schwannoma) and malignant Schwannoma, as well as tumours of the central nervous system such as brain and bone marrow tumours; intestinal cancer such as for example carcinoma of the rectum, colon carcinoma, colorectal carcinoma, anal carcinoma, carcinoma of the large bowel, tumours of the small intestine and duodenum; eyelid tumours such as basalioma or basal cell carcinoma; pancreatic cancer or carcinoma of the pancreas; bladder cancer or carcinoma of the bladder; lung cancer (bronchial carcinoma) such as for example small-cell bronchial carcinomas (oat cell carcinomas) and non-small cell bronchial carcinomas (NSCLC) such as plate epithelial carcinomas, adenocarcinomas and large-cell bronchial carcinomas; breast cancer such as for example mammary carcinoma such as infiltrating ductal carcinoma, colloid carcinoma, lobular invasive carcinoma, tubular carcinoma, adenocystic carcinoma and papillary carcinoma; non-Hodgkin's lymphomas (NHL) such as for example Burkitt's lymphoma, low-malignancy non-Hodgkin's lymphomas (NHL) and mucosis fungoides; uterine cancer or endometrial carcinoma or corpus carcinoma; CUP syndrome (Cancer of Unknown Primary); ovarian cancer or ovarian carcinoma such as mucinous, endometrial or serous cancer; gall bladder cancer; bile duct cancer such as for example Klatskin tumour; testicular cancer such as for example seminomas and non-seminomas; lymphoma (lymphosarcoma) such as for example malignant lymphoma, Hodgkin's disease, non-Hodgkin's lymphomas (NHL) such as chronic lymphatic leukaemia, leukaemic reticuloendotheliosis, immunocytoma, plasmocytoma (multiple myeloma), immunoblastoma, Burkitt's lymphoma, T-zone mycosis fungoides, large-cell anaplastic lymphoblastoma and lymphoblastoma; laryngeal cancer such as for example tumours of the vocal cords, supraglottal, glottal and subglottal laryngeal tumours; bone cancer such as for example osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, osteoma, osteoid osteoma, osteoblastoma, eosinophilic granuloma, giant cell tumour, chondrosarcoma, osteosarcoma, Ewing's sarcoma, reticulo-sarcoma, plasmocytoma, fibrous dysplasia, juvenile bone cysts and aneurysmatic bone cysts; head and neck tumours such as for example tumours of the lips, tongue, floor of the mouth, oral cavity, gums, palate, salivary glands, throat, nasal cavity, paranasal sinuses, larynx and middle ear; liver cancer such as for example liver cell carcinoma or hepatocellular carcinoma (HCC); leukaemias, such as for example acute leukaemias such as acute lymphatic/lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML); chronic leukaemias such as chronic lymphatic leukaemia (CLL), chronic myeloid leukaemia (CML); stomach cancer or gastric carcinoma such as for example papillary, tubular and mucinous adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, small-cell carcinoma and undifferentiated carcinoma; melanomas such as for example superficially spreading, nodular, lentigo-maligna and acral-lentiginous melanoma; renal cancer such as e.g.

kidney cell carcinoma or hypernephroma or Grawitz's tumour; oesophageal cancer or carcinoma of the oesophagus; penile cancer; prostate cancer; throat cancer or carcinomas of the pharynx such as for example nasopharynx carcinomas, oropharynx carcinomas and hypopharynx carcinomas; retinoblastoma; vaginal cancer or vaginal carcinoma; plate epithelial carcinomas, adenocarcinomas, *in situ* carcinomas, malignant melanomas and sarcomas; thyroid carcinomas

such as for example papillary, follicular and medullary thyroid carcinoma, as well as anaplastic carcinomas; spinalioma, epidormoid carcinoma and plate epithelial carcinoma of the skin; thymomas, cancer of the urethra and cancer of the vulva.

**[0261]** The new compounds may be used for the prevention, short-term or long-term treatment of the above-mentioned diseases, optionally also in combination with radiotherapy or other "state-of-the-art" compounds, such as e.g. cytostatic or cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances, steroids or antibodies.

**[0262]** The compounds of general formula (I) may be used on their own or in combination with other active substances according to the invention, optionally also in combination with other pharmacologically active substances.

**[0263]** Chemotherapeutic agents which may be administered in combination with the compounds according to the invention, include, without being restricted thereto, hormones, hormone analogues and antihormones (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol acetate, flutamide, nilutamide, bicalutamide, aminoglutethimide, cyproterone acetate, finasteride, buserelin acetate, fludrocortisone, fluoxymesterone, medroxyprogesterone, octreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, vorozole, exemestane, atamestane), LHRH agonists and antagonists (e.g. goserelin acetate, luproline), inhibitors of growth factors (growth factors such as for example "platelet derived growth factor (PDGF)", "fibroblast growth factor (FGF)", "vascular endothelial growth factor (VEGF)", "epidermal growth factor (EGF)", "insuline-like growth factors (IGF)", "human epidermal growth factor (HER, e.g. HER2, HER3, HER4)" and "hepatocyte growth factor (HGF)"), inhibitors are for example "growth factor" antibodies, "growth factor receptor" antibodies and tyrosine kinase inhibitors, such as for example cetuximab, gefitinib, imatinib, lapatinib and trastuzumab); antimetabolites (e.g. antifolates such as methotrexate, raltitrexed, pyrimidine analogues such as 5-fluorouracil, capecitabine and gemcitabine, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine, fludarabine); antitumour antibiotics (e.g. anthracyclins such as doxorubicin, daunorubicin, epirubicin and idarubicin, mitomycin-C, bleomycin, dactinomycin, plicamycin, streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin, carboplatin); alkylation agents (e.g. estramustine, meclorethamine, melphalan, chlorambucil, busulphan, dacarbazine, cyclophosphamide, ifosfamide, temozolomide, nitrosoureas such as for example carmustine and lomustine, thiopeta); antimitotic agents (e.g. Vinca alkaloids such as for example vinblastine, vindesine, vinorelbine and vincristine; and taxanes such as paclitaxel, docetaxel); tubuline inhibitors; PARP inhibitors, topoisomerase inhibitors (e.g. epipodophyllotoxins such as for example etoposide and etopophos, teniposide, amsacrine, topotecan, irinotecan, mitoxantrone), serine/threonine kinase inhibitors (e.g. PDK 1 inhibitors, B-Raf inhibitors, mTOR inhibitors, mTORC1 inhibitors, PI3K inhibitors, dual mTOR/PI3K inhibitors, STK 33 inhibitors, AKT inhibitors, PLK 1 inhibitors, inhibitors of CDKs, Aurora kinase inhibitors), tyrosine kinase inhibitors (e.g. PTK2/FAK inhibitors), protein protein interaction inhibitors (e.g. IAP, Mcl-1, MDM2/MDMX), MEK inhibitors, ERK inhibitors, IGF-1 R inhibitors, ErbB receptor inhibitors, rapamycin analogs (e.g. everolimus, temsirolimus, ridaforolimus, sirolimus) and various chemotherapeutic agents such as amifostine, anagrelide, clodronate, filgrastin, interferon, interferon alpha, leucovorin, rituximab, procarbazine, levamisole, mesna, mitotane, pamidronate and porfimer.

**[0264]** Other possible combination partners are 2-chlorodesoxyadenosine, 2-fluorodesoxycytidine, 2-methoxyoestradiol, 2C4, 3-alethine, 131-I-TM-601, 3CPA, 7-ethyl-10-hydroxycamptothecin, 16-aza-epothilone B, A 105972, A 204197, abiraterone, aldesleukin, alitretinoin, allovectin-7, altretamine, alvocidib, amonafide, anthrapyrazole, AG-2037, AP-5280, apaziquone, apomine, aranose, arglabin, arzoxifene, atamestane, atrasentan, auristatin PE, AVLb, AZ10992, ABX-EGF, AMG-479 (ganitumab), ARRY 162, ARRY 438162, ARRY-300, ARRY-142886/AZD-6244 (selumetinib), ARRY-704/ AZD-8330, AR-12, AR-42, AS-703988, AXL-1717, AZD-8055, AZD-5363, AZD-6244, ARQ-736, ARQ 680, AS-703026 (primasertib), avastin, AZD-2014, azacytidine, azaepothilone B, azonafide, BAY-43-9006, BAY 80-6946, BBR-3464, BBR-3576, bevacizumab, BEZ-235, biricodar dicitrate, BCX-1777, BKM-120, bleocin, BLP-25, BMS-184476, BMS-247550, BMS-188797, BMS-275291, BMS-663513, BMS-754807, BNP-1350, BNP-7787, BIBW 2992 (afatinib, tomtovok), BIBF 1120 (vargatef), BI 836845, BI 2536, BI 6727, BI 836845, BI 847325, BI 853520, BIIB-022, bleomycinic acid, bleomycin A, bleomycin B, brivanib, bryostatine-1, bortezomib, brostallicin, busulphan, BYL-719, CA-4 prodrug, CA-4, CapCell, calcitriol, canertinib, canfosfamide, capecitabine, carboxyphthaloplatin, CCI-779, CC-115, CC-223, CEP-701, CEP-751, CBT-1 cefixime, ceflatonin, ceftriaxone, celecoxib, celmoleukin, cemadotin, CH4987655/RO-4987655, chlorotrianisene, cilengitide, ciclosporin, CDA-II, CDC-394, CKD-602, CKI-27, clofarabine, colchicine, combretastatin A4, COT inhibitors, CHS-828, CH-5132799, CLL-Thera, CMT-3 cryptophycin 52, CTP-37, CTLA-4 monoclonal antibodies, CP-461, CV-247, cyanomorpholinodoxorubicin, cytarabine, D 24851, decitabine, deoxorubicin, deoxyrubicin, deoxycoformycin, depsiptide, desoxyepothilone B, dexamethasone, dexrazoxane, diethylstilbestrol, diflomotecan, didox, DM-DC, dolastatin 10, doranidazole, DS-7423, E7010, E-6201, edatrexat, edotreotide, efaproxiral, eflornithine, EGFR inhibitors, EKB-569, EKB-509, enzastaurin, elsamitrucin, epothilone B, epratuzumab, ER-86526, erlotinib, ET-18-OCH<sub>3</sub>, ethynylcytidine, ethynylloestradiol, exatecan, exatecan mesylate, exemestane, exisulind, fenretinide, figitumumab, floxuridine, folic acid, FOLFOX, FOLFOX4, FOLFIRI, formestane, fotemustine, galarubicin, gallium maltolate, gefitinib, gem-

tuzumab, gimatecan, glufosfamide, GCS-IOO, GDC-0623, GDC-0941 (pictrelisib), GDC-0980, GDC-0032, GDC-0068, GDC-0349, GDC-0879, G17DT immunogen, GMK, GPX-100, gp100-peptide vaccines, GSK-5126766, GSK-690693, GSK-1120212 (trametinib), GSK-2118436 (dabrafenib), GSK-2126458, GSK-2132231A, GSK-2334470, GSK-2110183, GSK-2141795, GW2016, granisetron, herceptine, hexamethylmelamine, histamine, homoharringtonine, hyaluronic acid, hydroxyurea, hydroxyprogesterone caproate, ibandronate, ibritumomab, idatrexate, idenestrol, IDN-5109, IGF-1R inhibitors, IMC-1C11, IMC-A12 (cixutumumab), immunol, indisulam, interferon alpha-2a, interferon alpha-2b, pegylated interferon alpha-2b, interleukin-2, INK-1117, INK-128, INSM-18, ionafarnib, ipilimumab, iproplatin, irofulven, isohomohalichondrin-B, isoflavone, isotretinoin, ixabepilone, JRX-2, JSF-154, J-107088, conjugated oestrogens, kahalid F, ketoconazole, KW-2170, KW-2450, lobaplatin, leflunomide, lenograstim, leuprolide, leuporelin, lexicronam, LGD-1550, linezolid, lutetium texaphyrin, lometrexol, losoxantrone, LU 223651, lurtotecan, LY-S6AKT1, LY-2780301, mafosfamide, marimastat, mechloroethamine, MEK inhibitors, MEK-162, methyltestosterone, methylprednisolone, MEDI-573, MEN-10755, MDX-H210, MDX-447, MDX-1379, MGX, midostaurin, minodronic acid, mitomycin, mivobulin, MK-2206, MK-0646 (dalotuzumab), MLN518, motexafin gadolinium, MS-209, MS-275, MX6, neridronate, neratinib, Nexavar, neovastat, nilotinib, nimesulide, nitroglycerin, nolatrexed, norelin, N-acetylcysteine, O6-benzylguanine, oblimersen, omeprazole, oncophage, oncoVEX<sup>GM-CSF</sup>, ormaplatin, ortataxel, OX44 antibodies, OSI-027, OSI-906 (linsitinib), 4-1BB antibodies, oxantrazole, oestrogen, panitumumab, patupilone, pegfilgrastim, PCK-3145, pegfilgrastim, PBI-1402, PBI-05204, PDO325901, PD-1 antibodies, PEG-paclitaxel, albumin-stabilized paclitaxel, PEP-005, PF-05197281, PF-05212384, PF-04691502, PHT-427, P-04, PKC412, P54, PI-88, pelitinib, pemetrexed, pentrix, perifosine, perillylalcohol, pertuzumab, PI3K inhibitors, PI3K/mTOR inhibitors, PG-TXL, P G 2, PLX-4032/RO-5185426 (vemurafenib), PLX-3603/RO-5212054, PT-100, PWT-33597, PX-866, picoplatin, pivaloyloxymethylbutyrate, pixantrone, phenoxodiol O, PK1166, plevitrexed, plicamycin, polyprenic acid, porfiromycin, prednisone, prednisolone, quinamed, quinupristin, R115777, RAF-265, ramosetron, ranpirnase, RDEA-119/BAY 869766, RDEA-436, rebeccamycin analogues, receptor tyrosine kinase (RTK) inhibitors, revimid, RG-7167, RG-7304, RG-7421, RG-7321, RG 7440, rhizoxin, rhu-MAb, rinfabate, risedronate, rituximab, robatumumab, rofecoxib, RO-31-7453, RO-5126766, RO-5068760, RPR 109881A, rubidazole, rubitecan, R-flurbiprofen, RX-0201, S-9788, sabarubicin, SAHA, sargramostim, satraplatin, SB 408075, Se-015/Ve-015, SU5416, SU6668, SDX-101, semustin, seocalcitol, SM-11355, SN-38, SN-4071, SR-27897, SR-31747, SR-13668, SRL-172, sorafenib, squalamine, suberanilohydroxamic acid, sutent, T 900607, T 138067, TAK-733, TAS-103, tacedinaline, talaporfin, Tarceva, tariquitar, tasisulam, taxotere, taxoprexin, tazarotene, tegafur, temozolamide, tesmilifene, testosterone, testosterone propionate, tesmilifene, tetraplatin, tetrodotoxin, tezacitabine, thalidomide, theralux, therarubicin, thymalfasin, thymectacin, tiazofurin, tipifamib, tirapazamine, tocladesine, tomudex, toremofin, trabectedin, Trans-MID-107, transretinic acid, traszutumab, tremelimumab, tretinoin, triacetyluridine, triapine, triciribine, trimetrexate, TLK-286TXD 258, tykerb/tyverb, urocidin, valrubicin, vatalanib, vincristine, vinflunine, virulizin, WX-UK1, WX-554, vectibix, xeloda, XELOX, XL-147, XL-228, XL-281, XL-518/R-7420/GDC-0973, XL-765, YM-511, YM-598, ZD-4190, ZD-6474, ZD-4054, ZD-0473, ZD-6126, ZD-9331, ZD1839, ZSTK-474, zoledronat and zoledronate.

**[0265]** Suitable preparations include for example tablets, capsules, suppositories, solutions - particularly solutions for injection (s.c., i.v., i.m.) and infusion - elixirs, emulsions or dispersible powders. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 90 wt.-%, preferably 0.5 to 50 wt.-% of the composition as a whole, i.e. in amounts which are sufficient to achieve the dosage range specified below. The doses specified may, if necessary, be given several times a day.

**[0266]** Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

**[0267]** Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

**[0268]** Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

**[0269]** Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

**[0270]** Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

**[0271]** Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

**[0272]** Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

**[0273]** The preparations are administered by the usual methods, preferably by oral or transdermal route, most preferably by oral route. For oral administration the tablets may, of course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tableting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

**[0274]** For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

**[0275]** The dosage for intravenous use is from 1 - 1000 mg per hour, preferably between 5 and 500 mg per hour.

**[0276]** However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

**[0277]** The formulation examples which follow illustrate the present invention without restricting its scope:

#### Examples of pharmaceutical formulations

##### **[0278]**

A) Tablets	per tablet
active substance according to formula (I)	100 mg
lactose	140 mg
corn starch	240 mg
polyvinylpyrrolidone	15 mg
magnesium stearate	5 mg
	<hr/> 500 mg

**[0279]** The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B) Tablets	per tablet
active substance according to formula (I)	80 mg
lactose	55 mg
corn starch	190 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone	15 mg
sodium-carboxymethyl starch	23 mg
magnesium stearate	2 mg
	<hr/> 400 mg

**[0280]** The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvi-

nylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodiumcarboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

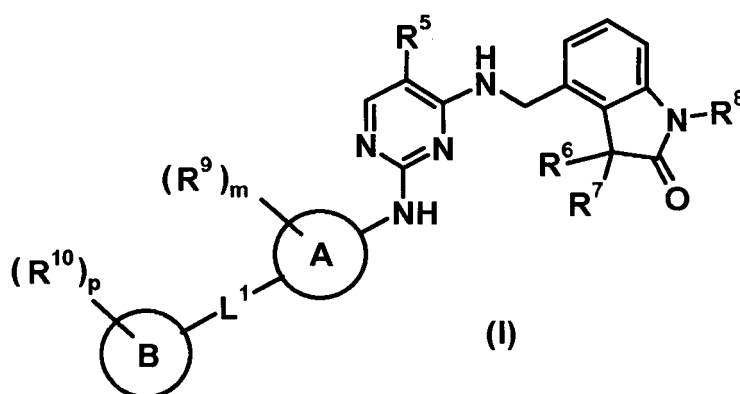
C) Ampoule solution

active substance according to formula (I)	50 mg
sodium chloride	50 mg
water for inj.	5 mL

**[0281]** The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

### Claims

1. Compounds of general formula (I)



wherein

$R^5$  is selected from among trifluoromethyl and halogen;

$R^6$ ,  $R^7$  and  $R^8$  are independently selected in each case from among hydrogen and  $C_{1-4}$ alkyl or

$R^6$  and  $R^7$  together with the carbon atom to which they bond form a saturated, 3-5 membered hydrocarbon ring; ring system **A** is selected from among  $C_{6-10}$ aryl, 3-14 membered heterocyclyl and 5-12 membered heteroaryl; each  $R^9$  is independently selected in each case from among  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ haloalkoxy, halogen and -CN;

m denotes 0, 1, 2 or 3;

$L^1$  is selected from among a bond,  $-(CH_2)_n-O$ ,  $-(CH_2)_n-NH$ ,  $-(CH_2)_n-NH-C(O)$ ,  $-(CH_2)_n-C(O)-NH$ ,  $-(CH_2)_n-$  and  $-(CH_2)_n-C(O)$ , while in the present nomenclature the linker group  $L^1$  on the right binds to the ring system **A**;

n denotes 0, 1, 2 or 3;

ring system **B** is selected from among 4-10 membered, saturated or unsaturated heterocyclyl and phenyl;

each  $R^{10}$  is independently selected in each case from among  $R^a$  and  $R^b$ ;

p denotes 0, 1, 2 or 3;

each  $R^a$  independently denotes a group optionally substituted by one or more identical or different  $R^b$  and/or  $R^c$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

each  $R^b$  is independently selected in each case from among  $-OR^c$ ,  $-SR^c$ ,  $-NR^cR^c$ , halogen, -CN,  $-NO_2$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-C(NR^f)NR^cR^c$ ,  $-OC(O)R^c$ ,  $-OC(O)OR^c$ ,  $-S(O)_2R^c$ ,  $-S(O)_2NR^cR^c$ ,  $-NR^fC(O)R^c$ ,  $-NR^fC(O)OR^c$ ,  $-NR^fC(O)NR^cR^c$ ,  $-NR^fC(NR^f)NR^cR^c$  and  $-NR^fS(O)_2R^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;



each  $R^c$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^d$  and/or  $R^e$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl;

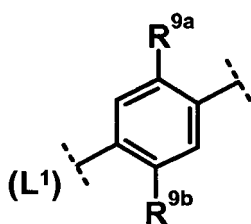
each  $R^d$  is independently selected in each case from among  $-OR^e$ ,  $-SR^e$ ,  $-NR^eR^e$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$ ,  $-C(O)NR^eR^e$ ,  $-C(NR^f)NR^eR^e$ ,  $-OC(O)R^e$ ,  $-OC(O)OR^e$ ,  $-S(O)_2R^e$ ,  $-S(O)_2NR^eR^e$ ,  $-NR^fC(O)R^e$ ,  $-NR^fC(O)OR^e$ ,  $-NR^fC(O)NR^eR^e$ ,  $-NR^fC(NR^f)NR^eR^e$  and  $-NR^fS(O)_2R^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

each  $R^e$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^f$  selected from among  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-10}$ cycloalkyl,  $C_{4-10}$ cycloalkenyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl, and

each  $R^f$  is independently selected in each case from among hydrogen and  $C_{1-6}$ alkyl,

while the compounds (I) may optionally also occur in the form of their tautomers, racemates, enantiomers, diastereomers or mixtures thereof, or as the respective salts of all the above-mentioned forms.

2. Compounds according claim 1, wherein ring system **A** is selected from among phenyl and 5-6 membered heteroaryl.
3. Compounds according to one of claims 1 or 2, wherein m has the value 0.
4. Compounds according to one of claims 1 or 2, wherein m has the value 1 or 2 and  $R^9$  is selected from among halogen,  $C_{1-4}$ alkyl and  $C_{1-4}$ alkoxy.
5. Compounds according to one of claims 1 to 4, wherein ring system **A** and the m groups  $R^9$  together denote



$R^{9a}$  is selected from among hydrogen,  $C_{1-4}$ alkyl and  $C_{1-4}$ alkoxy and

$R^{9b}$  is selected from among hydrogen and  $C_{1-4}$ alkyl.

6. Compounds according to one of claims 1 to 5, wherein  $L^1$  is selected from among a bond,  $-(CH_2)_2-O$ ,  $-NH-C(O)$ ,  $-C(O)-NH$ - and  $-C(O)$ , while in the present nomenclature the linker group  $L^1$  on the right binds to the ring system **A**.
7. Compounds according to one of claims 1 to 6, wherein ring system **B** is a 4-10 membered, saturated or unsaturated heterocyclyl.
8. Compounds according to one of claims 1 to 7, wherein p has the value 0.
9. Compounds according to one of claims 1 to 7, wherein p has the value 1 or 2, each  $R^{10}$  is independently selected in each case from among  $R^a$  and  $R^b$ ; each  $R^a$  independently denotes a group optionally substituted by one or more identical or different  $R^b$  and/or  $R^c$  selected from among  $C_{1-6}$ alkyl,  $C_{3-10}$ cycloalkyl and 3-14 membered heterocyclyl; each  $R^b$  is independently selected in each case from among  $-OR^c$ ,  $-NR^cR^c$ , halogen,  $-CN$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-S(O)_2R^c$  and  $-S(O)_2NR^cR^c$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems; each  $R^c$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^d$  and/or  $R^e$  selected from among  $C_{1-6}$ alkyl,  $C_{3-10}$ cycloalkyl, 5-12 membered heteroaryl and 3-14 membered hetero-

cyclyl;

each  $R^d$  is independently selected in each case from among  $-OR^e$ ,  $-NR^eR^e$ ,  $-CN$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$  and  $-NR^fC(O)OR^e$ , as well as the bivalent substituent  $=O$ , while the latter may only be a substituent in non-aromatic ring systems;

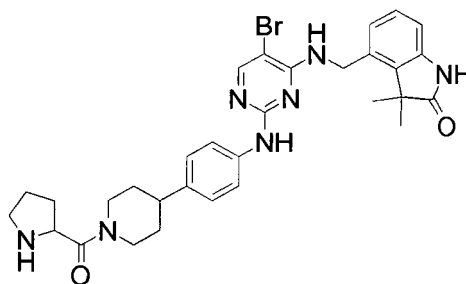
each  $R^e$  independently denotes hydrogen or a group optionally substituted by one or more identical or different  $R^f$  selected from among  $C_{1-6}$ alkyl,  $C_{6-10}$ aryl, 5-12 membered heteroaryl and 3-14 membered heterocyclyl, and each  $R^f$  is independently selected in each case from among hydrogen and  $C_{1-6}$ alkyl.

10. Compounds according to one of claims 1 or 9, wherein

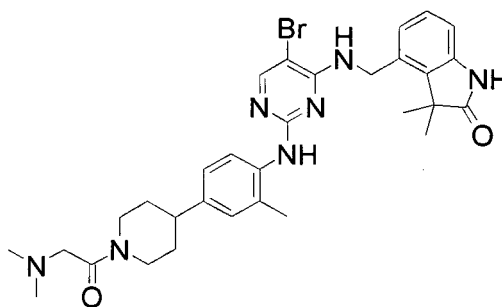
$p$  has the value 1.

11. Compounds according to claim 1 - or pharmaceutically acceptable salts thereof - selected from among:

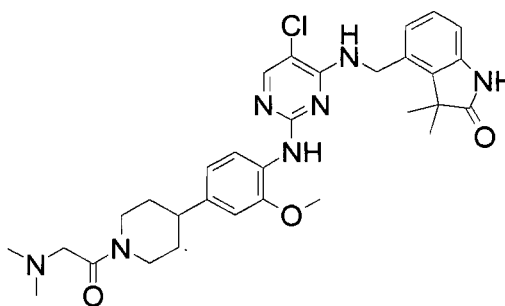
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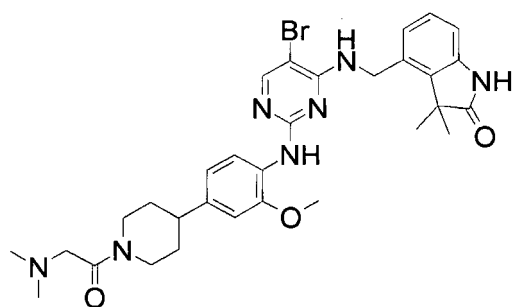
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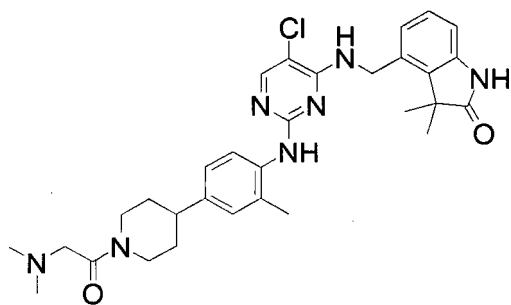
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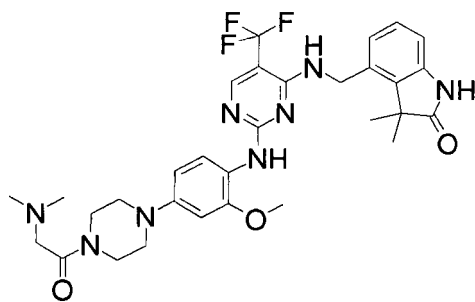
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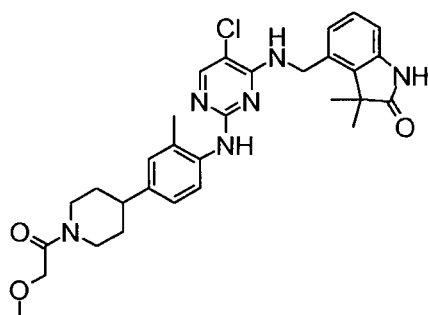
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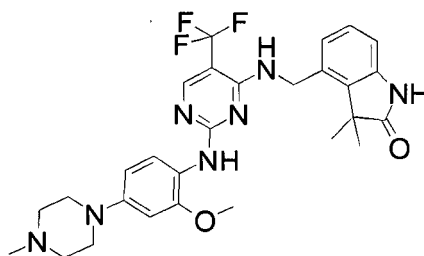
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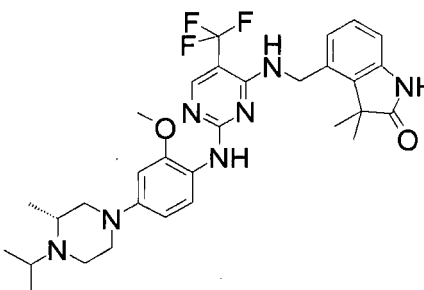
CN1C(=O)c2ccccc2CN1c3nc(Cl)c4c3nc(NC5=CC=C(C=C5)C6=CC=CC=C6C7=CC=CC=C7C8=CC=C(C=C8)OC9=CC=C(C=C9)N10CCNCC10)c4CCN1CCN(CC1)c2ccc(Oc3nc(Cl)c(NCc4c(C)cc(C(=O)N)c4)c5nnc35)cc2CN1C(=O)c2ccccc2C1NC3=NC=NC(NC4=CC=C(C=C4)C5=CC(OC)=CC=C5C6CCNCC6)C3=NC=C(Cl)N4CN1CCCC1c2ccc(NC3=NC=NC(Br)=N3)cc2C4=CC=C(C5C(C)(C)C(=O)N5)C=C4

140

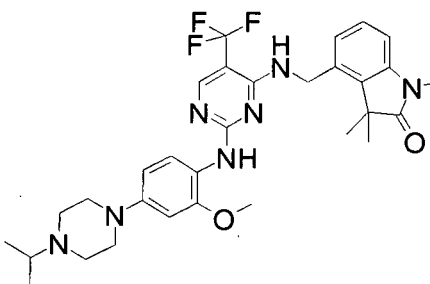
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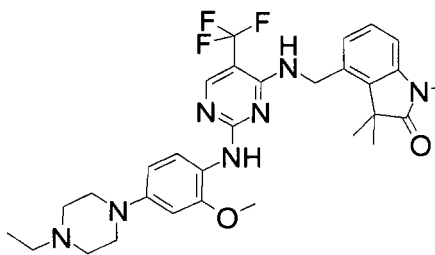
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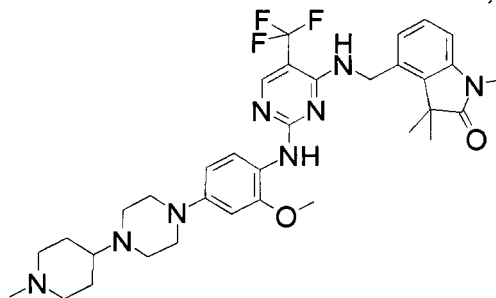
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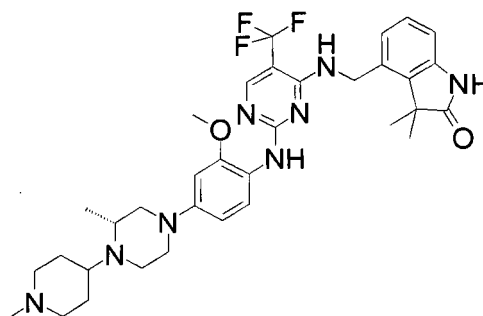
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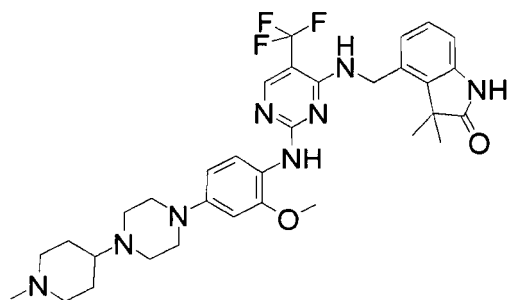
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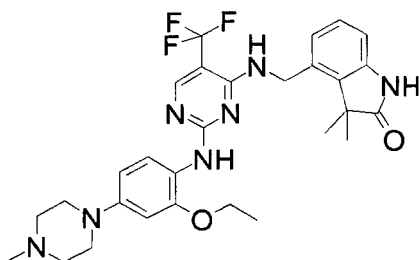
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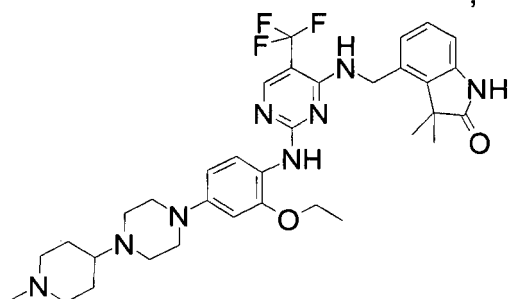
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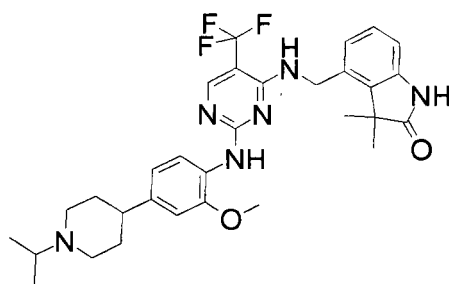
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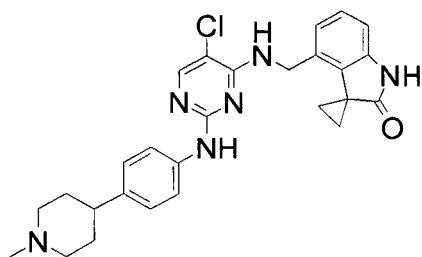
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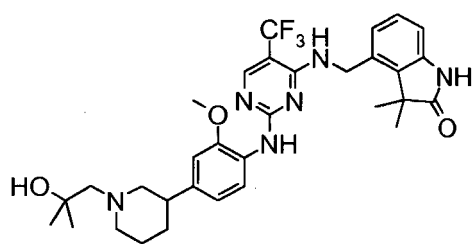
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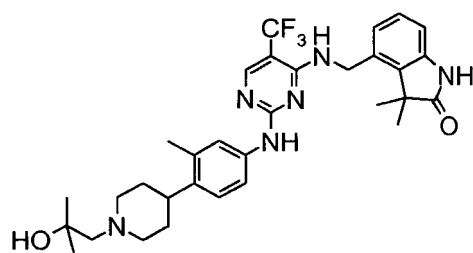
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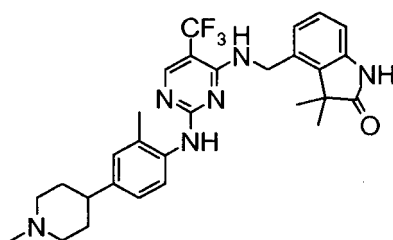
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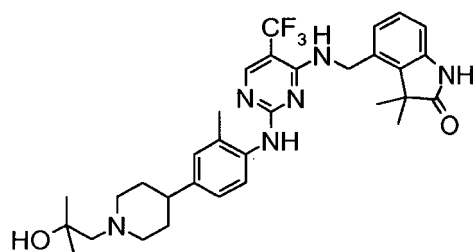
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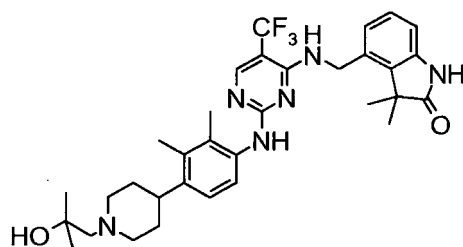
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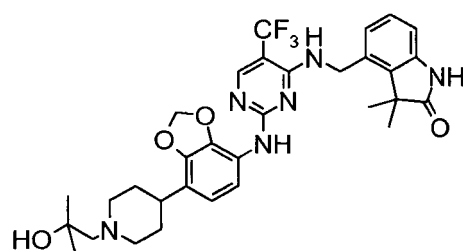
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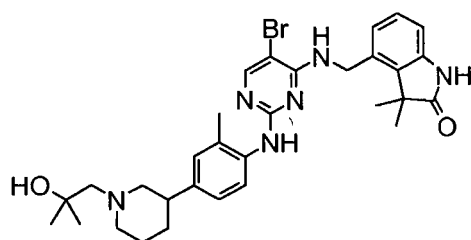
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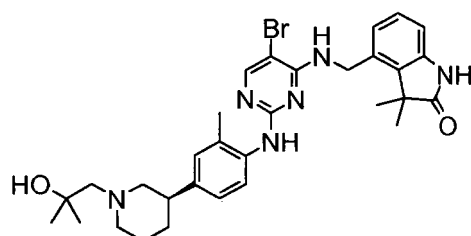
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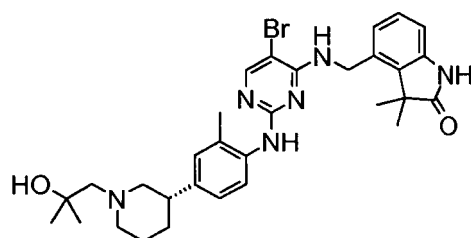
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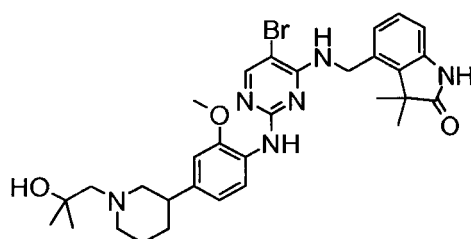
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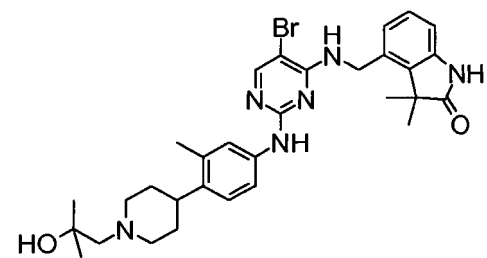
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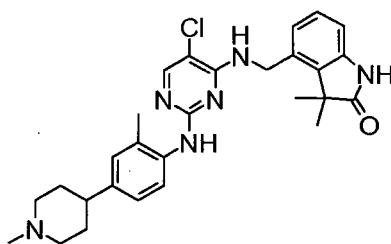


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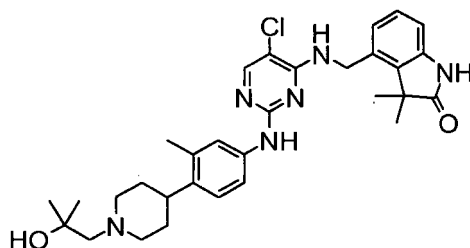




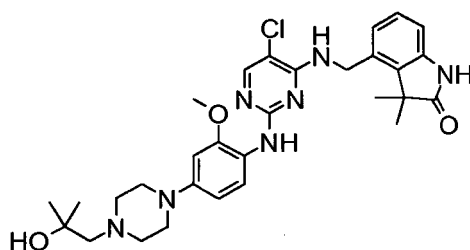
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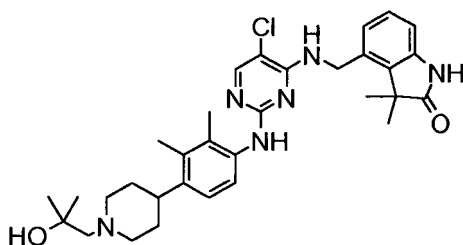
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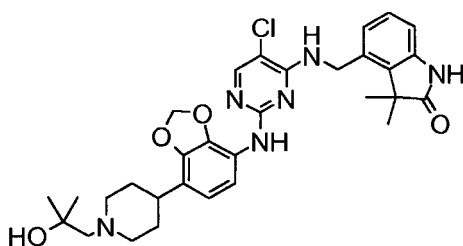
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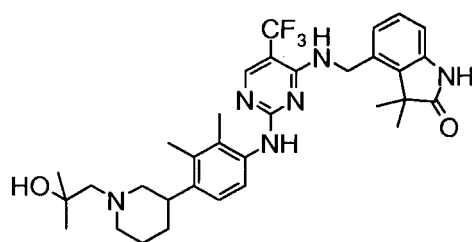
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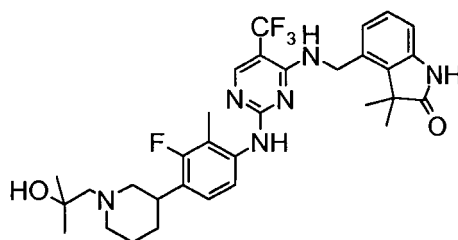
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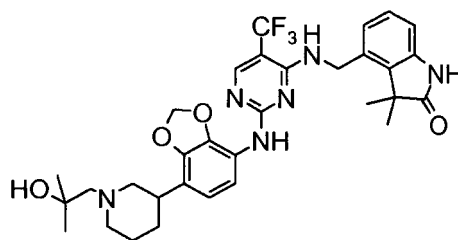
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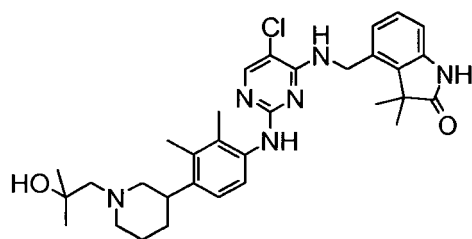
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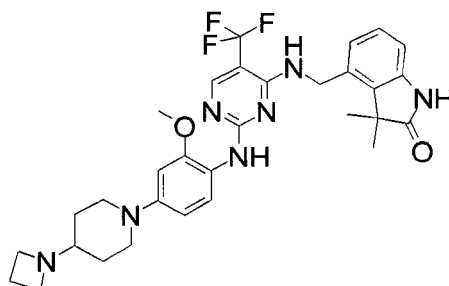
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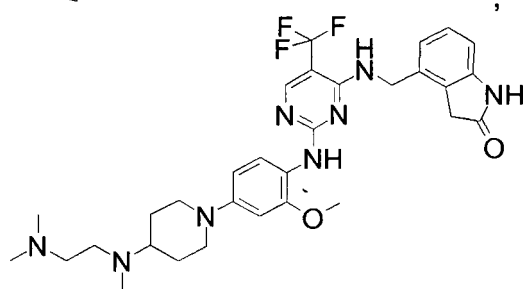
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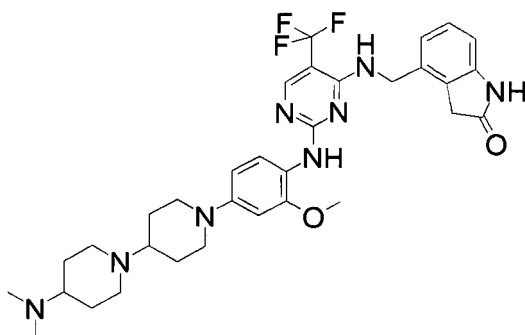
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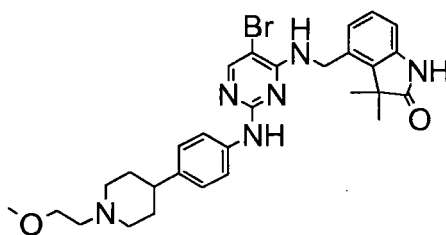
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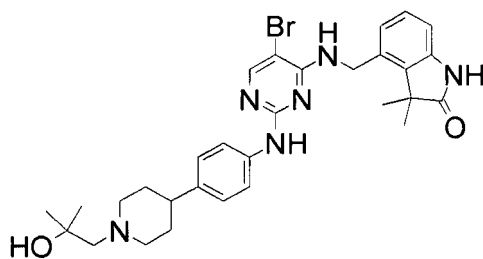
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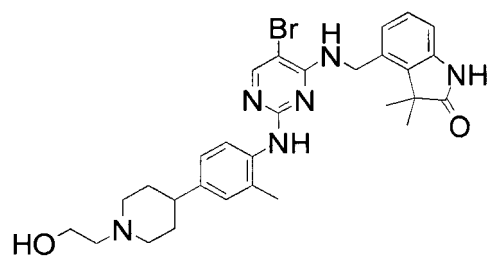
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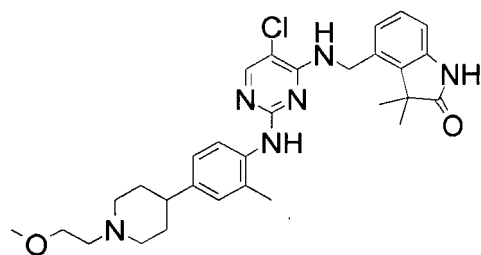
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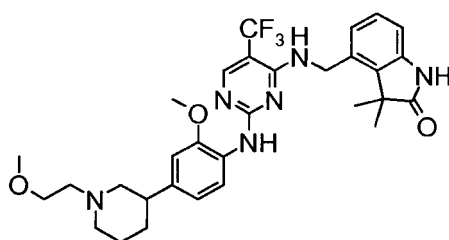
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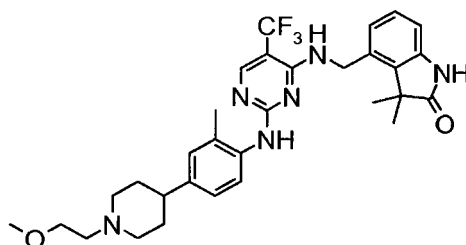
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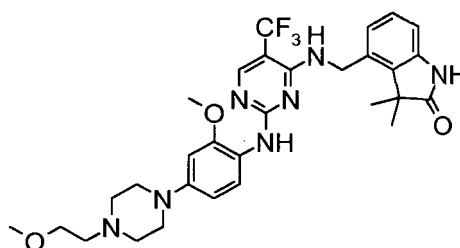
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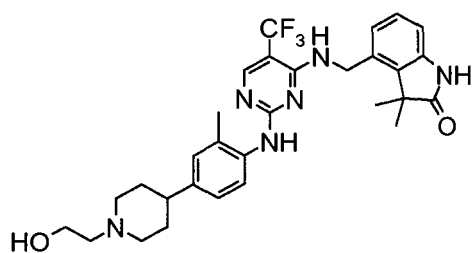
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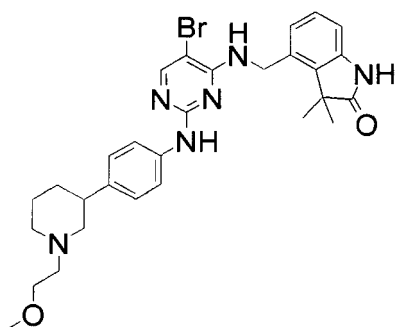
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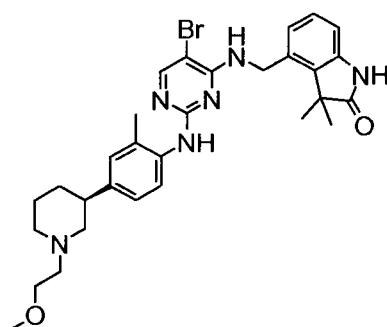
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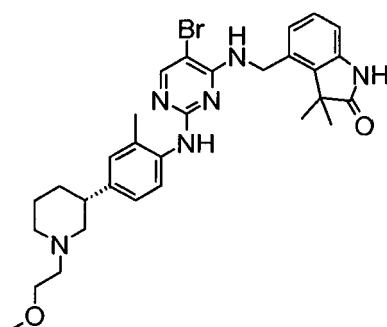
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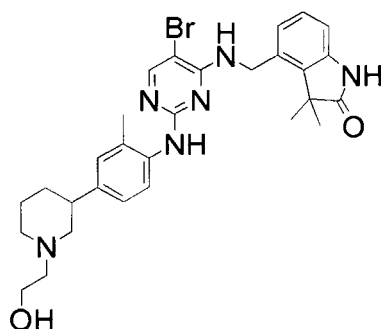
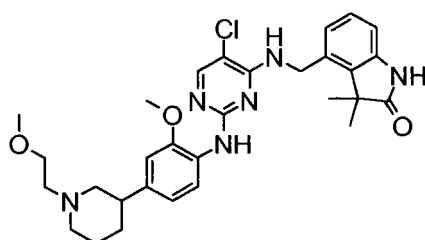
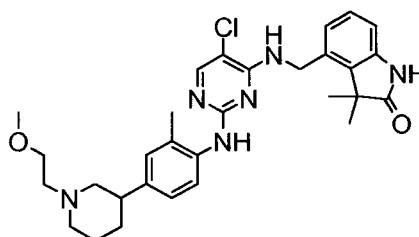


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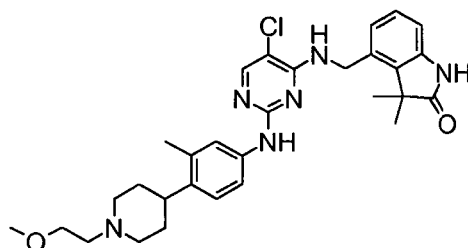


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**I-364****I-371****I-373**

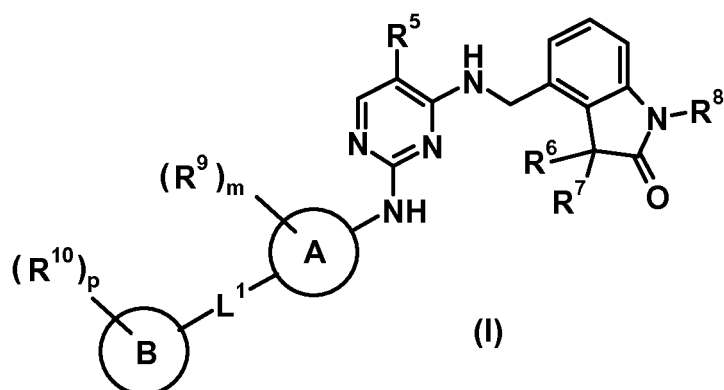
and

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12. Compounds of general formula (I) according to one of claims 1 to 11 - or the pharmaceutically acceptable salts thereof - for use as medicaments.
13. Compounds of general formula (I) according to one of claims 1 to 11 - or the pharmaceutically acceptable salts thereof - for use in the treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases.
14. Pharmaceutical preparation containing as active substance one or more compounds of general formula (I) according to one of claims 1 to 11 - or the pharmaceutically acceptable salts thereof - optionally in combination with conventional excipients and/or carriers.
15. Pharmaceutical preparation comprising a compound of general formula (I) according to one of claims 1 to 11 - or one of the pharmaceutically acceptable salts thereof - and at least one other cytostatic or cytotoxic active substance, different from formula (I).

## Patentansprüche

## 1. Verbindungen der allgemeinen Formel (I)



worin

$R^5$  ausgewählt ist aus Trifluormethyl und Halogen;

$R^6$ ,  $R^7$  und  $R^8$  jeweils unabhängig ausgewählt sind aus Wasserstoff und  $C_{1-4}$ Alkyl oder

$R^6$  und  $R^7$  zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen gesättigten, 3-5-gliedrigen Kohlenwasserstoffring bilden;

Ringsystem **A** ausgewählt ist aus  $C_{6-10}$ Aryl, 3-14-gliedrigem Heterocycl und 5-12-gliedrigem Heteroaryl;

jedes  $R^9$  jeweils unabhängig ausgewählt ist aus  $C_{1-6}$ Alkyl,  $C_{1-6}$ Halogenalkyl,  $C_{1-6}$ Alkoxy,  $C_{1-6}$ Halogenalkoxy, Halogen und -CN;

$m$  0, 1, 2 oder 3 bedeutet;

$L^1$  ausgewählt ist aus einer Bindung,  $-(CH_2)_n-O$ ,  $-(CH_2)_n-NH$ ,  $-(CH_2)_n-NH-C(O)$ ,  $-(CH_2)_n-C(O)-NH$ ,  $-(CH_2)_n$ - und  $-(CH_2)_n-C(O)$ , wobei in der vorliegenden Nomenklatur die Verknüpfungsgruppe  $L^1$  rechter Hand an das Ringsystem **A** bindet;

$n$  0, 1, 2 oder 3 bedeutet;

Ringsystem **B** ausgewählt ist aus 4-10-gliedrigem, gesättigtem oder ungesättigtem Heterocycl und Phenyl;

jedes  $R^{10}$  jeweils unabhängig ausgewählt ist aus  $R^a$  und  $R^b$ ;

$p$  0, 1, 2 oder 3 bedeutet;

jedes  $R^a$  unabhängig eine Gruppe gegebenenfalls substituiert durch ein oder mehrere gleiche oder verschiedene  $R^b$  und/oder  $R^c$  ausgewählt aus  $C_{1-6}$ Alkyl,  $C_{2-6}$ Alkenyl,  $C_{2-6}$ Alkynyl,  $C_{3-10}$ Cycloalkyl,  $C_{4-10}$ Cycloalkenyl,  $C_{6-10}$ Aryl, 5-12-gliedrigem Heteroaryl und 3-14-gliedrigem Heterocycl bedeutet;

jedes  $R^b$  jeweils unabhängig ausgewählt ist aus  $-OR^c$ ,  $-SR^c$ ,  $-NR^cR^c$ , Halogen, -CN,  $-NO_2$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-C(NR^f)NR^cR^c$ ,  $-OC(O)R^c$ ,  $-OC(O)OR^c$ ,  $-S(O)_2R^c$ ,  $-S(O)_2NR^cR^c$ ,  $-NR^fC(O)R^c$ ,  $-NR^fC(O)OR^c$ ,  $-NR^fC(O)NR^cR^c$ ,  $-NR^fC(NR^f)NR^cR^c$  und  $-NR^fS(O)_2R^c$ , ebenso wie dem zweiwertigen Substituenten =O, wobei Letzterer nur ein Substituent in nicht-aromatischen Ringsystemen sein kann;

jedes  $R^c$  unabhängig Wasserstoff oder eine Gruppe gegebenenfalls substituiert durch ein oder mehrere gleiche oder verschiedene  $R^d$  und/oder  $R^e$  ausgewählt aus  $C_{1-6}$ Alkyl,  $C_{2-6}$ Alkenyl,  $C_{2-6}$ Alkynyl,  $C_{3-10}$ Cycloalkyl,  $C_{4-10}$ Cycloalkenyl,  $C_{6-10}$ Aryl, 5-12-gliedrigem Heteroaryl und 3-14-gliedrigem Heterocycl bedeutet;

jedes  $R^d$  jeweils unabhängig ausgewählt ist aus  $-OR^e$ ,  $-SR^e$ ,  $-NR^eR^e$ , Halogen, -CN,  $-NO_2$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$ ,  $-C(O)NR^eR^e$ ,  $-C(NR^f)NR^eR^e$ ,  $-OC(O)R^e$ ,  $-OC(O)OR^e$ ,  $-S(O)_2R^e$ ,  $-S(O)_2NR^eR^e$ ,  $-NR^fC(O)R^e$ ,  $-NR^fC(O)OR^e$ ,  $-NR^fC(O)NR^eR^e$ ,  $-NR^fC(NR^f)NR^eR^e$  und  $-NR^fS(O)_2R^e$ , ebenso wie dem zweiwertigen Substituenten =O, wobei Letzterer nur ein Substituent in nicht-aromatischen Ringsystemen sein kann;

jedes  $R^e$  unabhängig Wasserstoff oder eine Gruppe gegebenenfalls substituiert durch ein oder mehrere gleiche oder verschiedene  $R^f$  ausgewählt aus  $C_{1-6}$ Alkyl,  $C_{2-6}$ Alkenyl,  $C_{2-6}$ Alkynyl,  $C_{3-10}$ Cycloalkyl,  $C_{4-10}$ Cycloalkenyl,  $C_{6-10}$ Aryl, 5-12-gliedrigem Heteroaryl und 3-14-gliedrigem Heterocycl bedeutet, und

jedes  $R^f$  jeweils unabhängig ausgewählt ist aus Wasserstoff und  $C_{1-6}$ Alkyl,

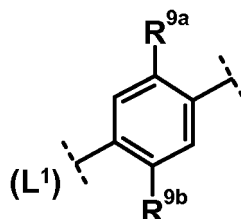
wobei die Verbindungen (I) gegebenenfalls auch in der Form ihrer Tautomere, Racemate, Enantiomere, Diastereomere oder Mischungen davon, oder als die betreffenden Salze von allen der vorstehend genannten Formen auftreten können.

2. Verbindungen nach Anspruch 1, worin Ringsystem **A** ausgewählt ist aus Phenyl und 5-6-gliedrigem Heteroaryl.

3. Verbindungen nach einem der Ansprüche 1 oder 2, worin **m** den Wert 0 aufweist.

4. Verbindungen nach einem der Ansprüche 1 oder 2, worin **m** den Wert 1 oder 2 aufweist und **R**<sup>9</sup> ausgewählt ist aus Halogen, C<sub>1-4</sub>Alkyl und C<sub>1-4</sub>Alkoxy.

5. Verbindungen nach einem der Ansprüche 1 bis 4, worin Ringsystem **A** und die **m** Gruppen **R**<sup>9</sup> zusammen



bedeuten, **R**<sup>9a</sup> ausgewählt ist aus Wasserstoff, C<sub>1-4</sub>Alkyl und C<sub>1-4</sub>Alkoxy und **R**<sup>9b</sup> ausgewählt ist aus Wasserstoff und C<sub>1-4</sub>Alkyl.

6. Verbindungen nach einem der Ansprüche 1 bis 5, worin **L**<sup>1</sup> ausgewählt ist aus einer Bindung, -(CH<sub>2</sub>)<sub>2</sub>-O-, -NH-C(O)-, -C(O)-NH- und -C(O), wobei in der vorliegenden Nomenklatur die Verknüpfungsgruppe **L**<sup>1</sup> rechter Hand an das Ringsystem **A** bindet.

7. Verbindungen nach einem der Ansprüche 1 bis 6, worin Ringsystem **B** ein 4-10-gliedriges, gesättigtes oder ungesättigtes Heterocyclyl ist.

8. Verbindungen nach einem der Ansprüche 1 bis 7, worin **p** den Wert 0 aufweist.

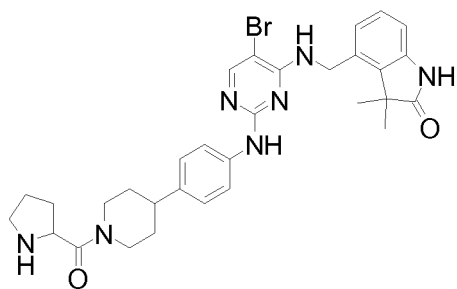
9. Verbindungen nach einem der Ansprüche 1 bis 7, worin **p** den Wert 1 oder 2 aufweist, jedes **R**<sup>10</sup> jeweils unabhängig ausgewählt ist aus **R**<sup>a</sup> und **R**<sup>b</sup>; jedes **R**<sup>a</sup> unabhängig eine Gruppe gegebenenfalls substituiert durch ein oder mehrere gleiche oder verschiedene **R**<sup>b</sup> und/oder **R**<sup>c</sup> ausgewählt aus C<sub>1-6</sub>Alkyl, C<sub>3-10</sub>Cycloalkyl und 3-14-gliedrigem Heterocyclyl bedeutet; jedes **R**<sup>b</sup> jeweils unabhängig ausgewählt ist aus -OR<sup>c</sup>, -NR<sup>c</sup>R<sup>c</sup>, Halogen, -CN, -C(O)R<sup>c</sup>, -C(O)OR<sup>c</sup>, -C(O)NR<sup>c</sup>R<sup>c</sup>, -S(O)<sub>2</sub>R<sup>c</sup> und -S(O)<sub>2</sub>NR<sup>c</sup>R<sup>c</sup>, ebenso wie dem zweiwertigen Substituenten =O, wobei Letzterer nur ein Substituent in nicht-aromatischen Ringsystemen sein kann; jedes **R**<sup>c</sup> unabhängig Wasserstoff oder eine Gruppe gegebenenfalls substituiert durch ein oder mehrere gleiche oder verschiedene **R**<sup>d</sup> und/oder **R**<sup>e</sup> ausgewählt aus C<sub>1-6</sub>Alkyl, C<sub>3-10</sub>Cycloalkyl, 5-12-gliedrigem Heteroaryl und 3-14-gliedrigem Heterocyclyl bedeutet; jedes **R**<sup>d</sup> jeweils unabhängig ausgewählt ist aus -OR<sup>e</sup>, -NR<sup>e</sup>R<sup>e</sup>, -CN, -C(O)R<sup>e</sup>, -C(O)OR<sup>e</sup> und -NR<sup>f</sup>C(O)OR<sup>e</sup>, ebenso wie dem zweiwertigen Substituenten =O, wobei Letzterer nur ein Substituent in nicht-aromatischen Ringsystemen sein kann; jedes **R**<sup>e</sup> unabhängig Wasserstoff oder eine Gruppe gegebenenfalls substituiert durch ein oder mehrere gleiche oder verschiedene **R**<sup>f</sup> ausgewählt aus C<sub>1-6</sub>Alkyl, C<sub>6-10</sub>Aryl, 5-12-gliedrigem Heteroaryl und 3-14-gliedrigem Heterocyclyl bedeutet, und jedes **R**<sup>f</sup> jeweils unabhängig ausgewählt ist aus Wasserstoff und C<sub>1-6</sub>Alkyl.

10. Verbindungen nach einem der Ansprüche 1 oder 9, worin **p** den Wert 1 aufweist.

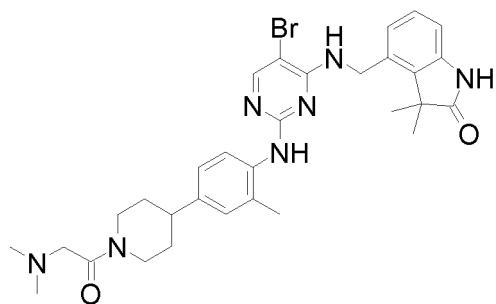
11. Verbindungen nach Anspruch 1 - oder pharmazeutisch akzeptable Salze davon - ausgewählt aus:



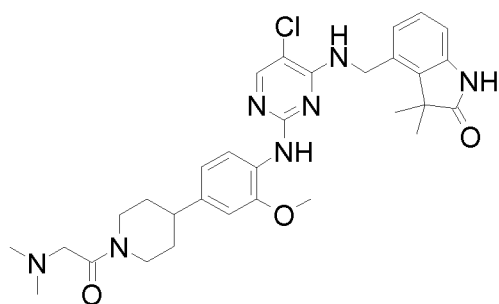
I-55



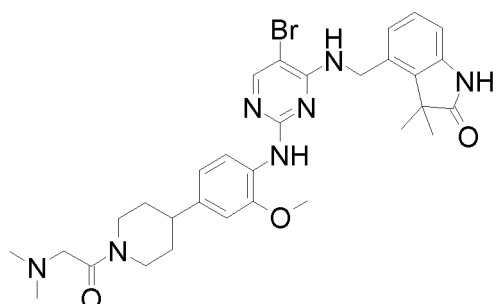
I-57



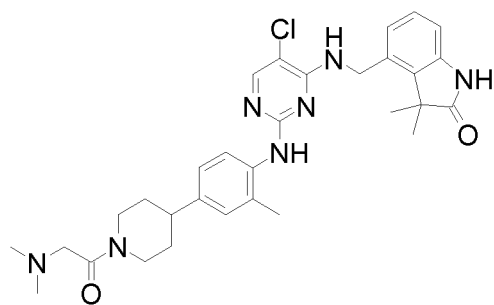
I-58



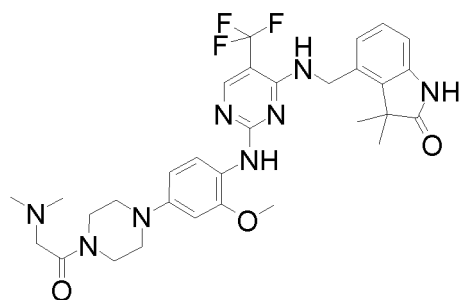
I-68



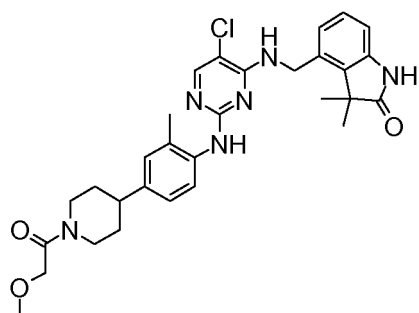
I-69



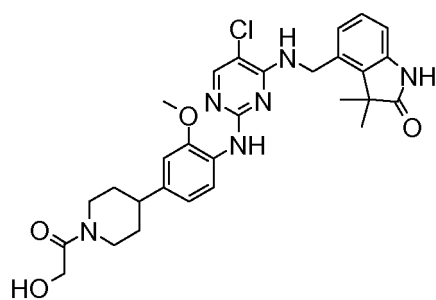
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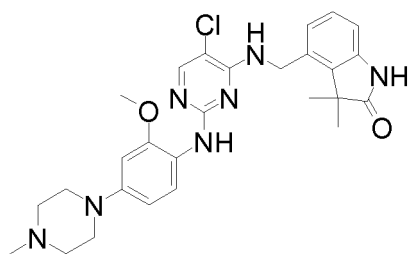
I-292



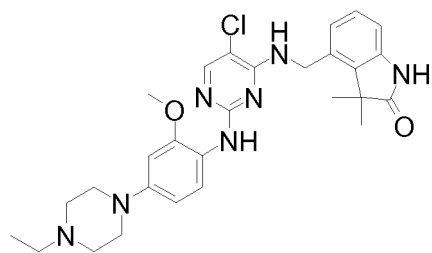
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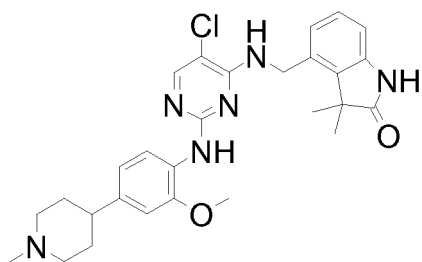
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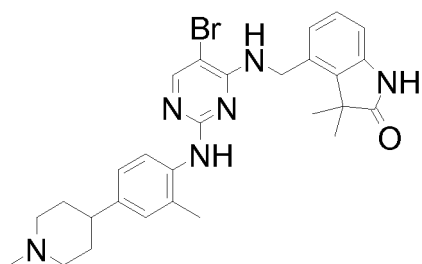
I-99



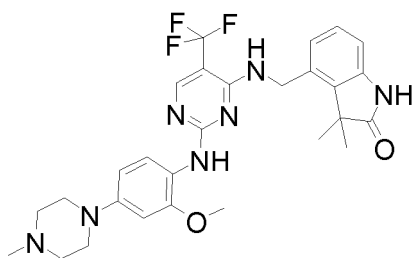
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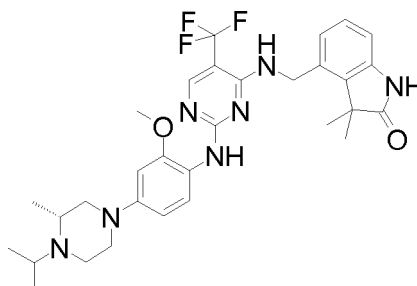
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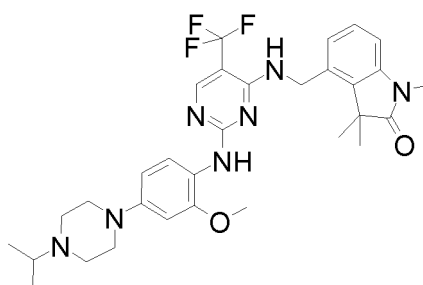
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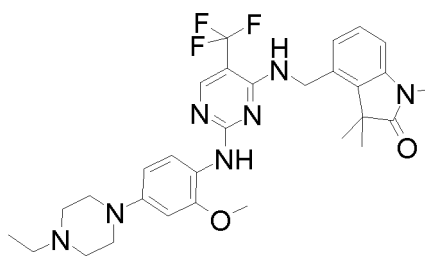
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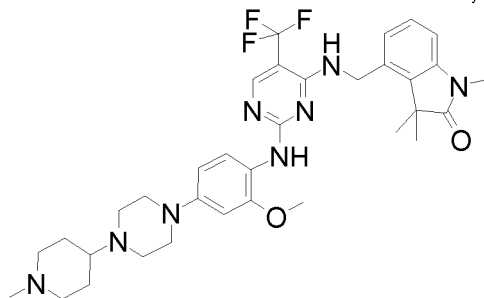
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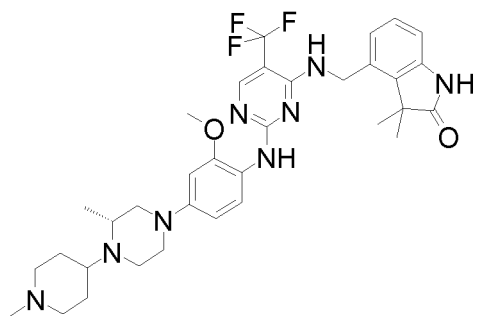
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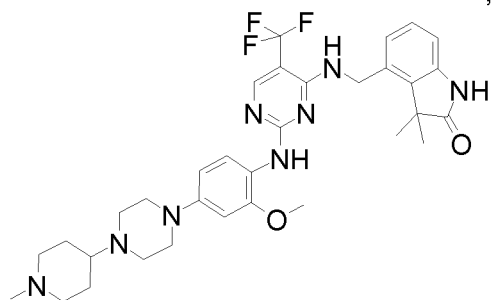
I-130



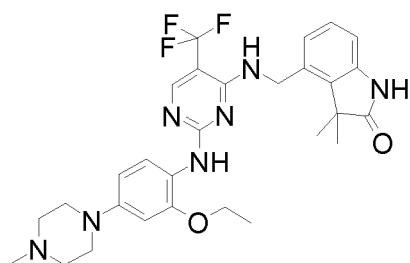
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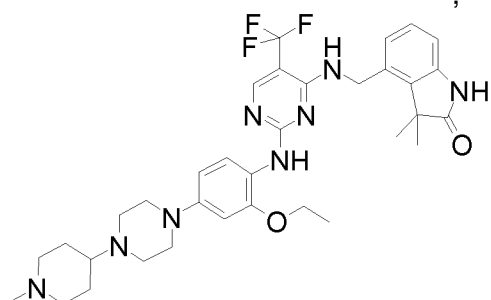
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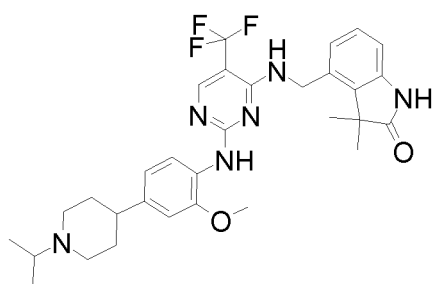
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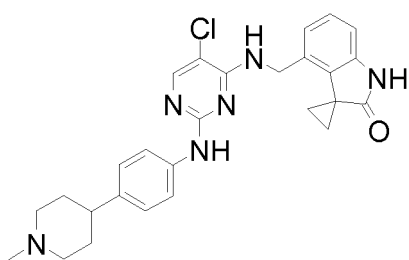
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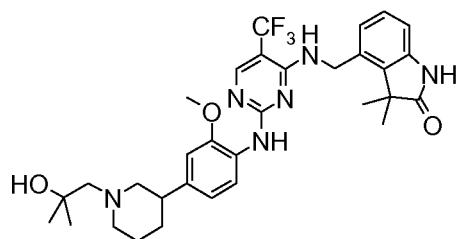
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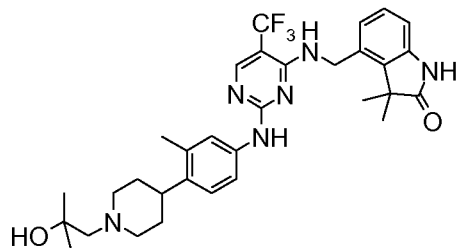
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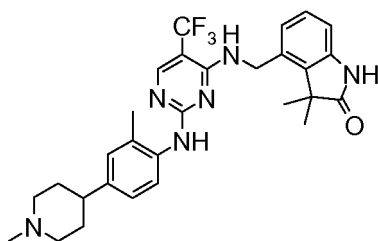
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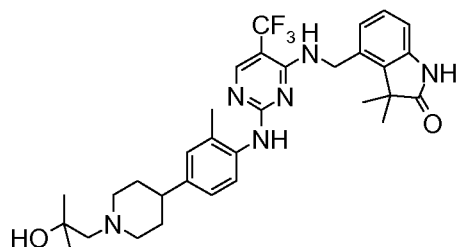
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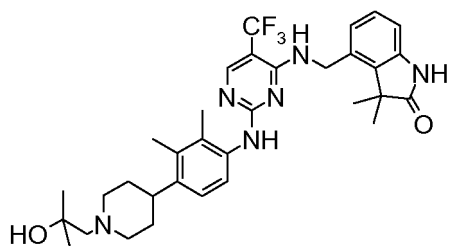
I-308



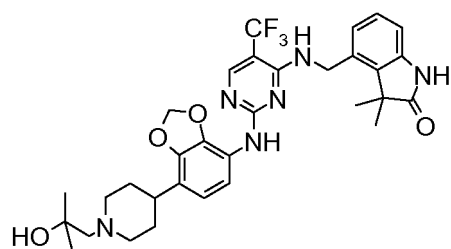
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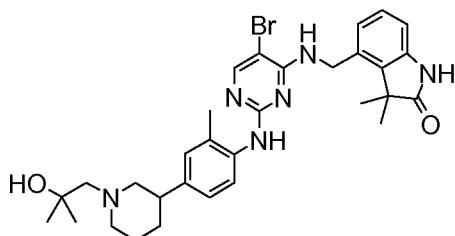
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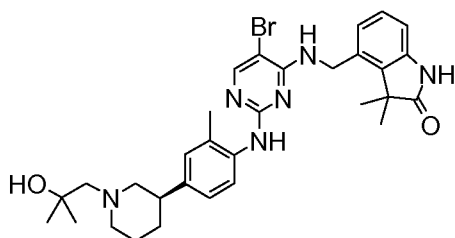
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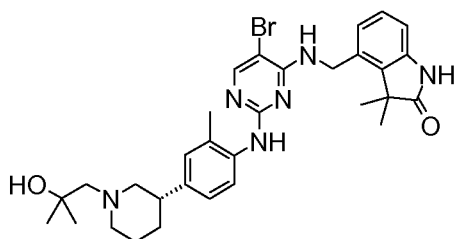
I-318



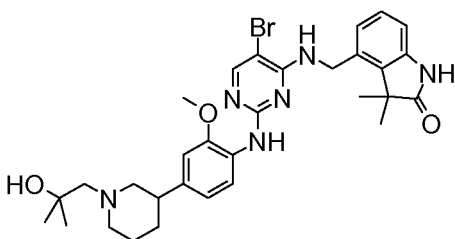
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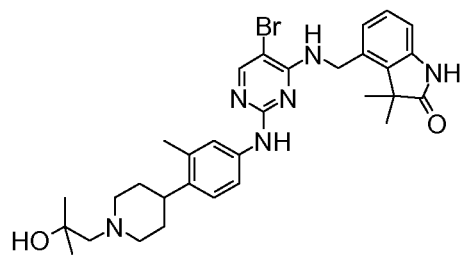
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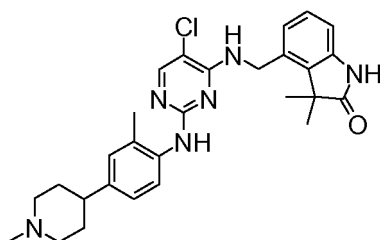
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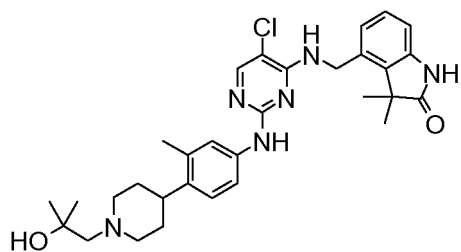
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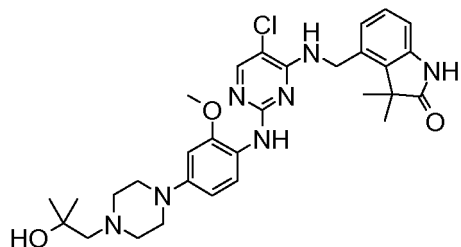
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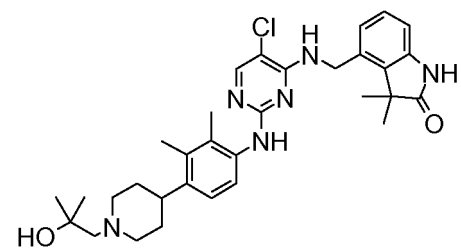
I-334



I-335



I-339





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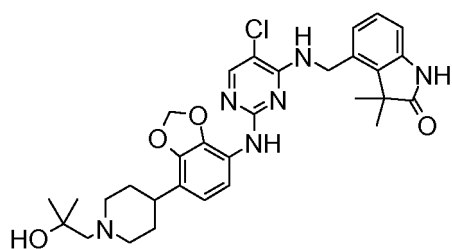
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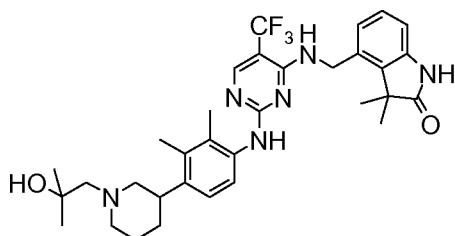
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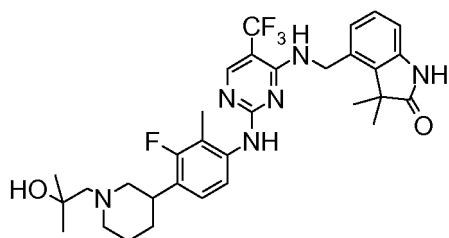
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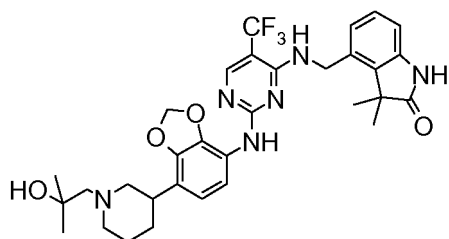
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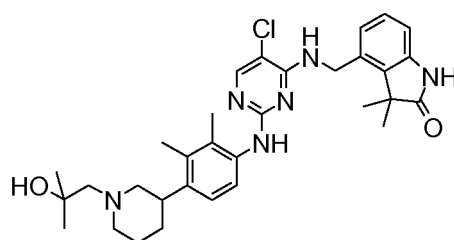
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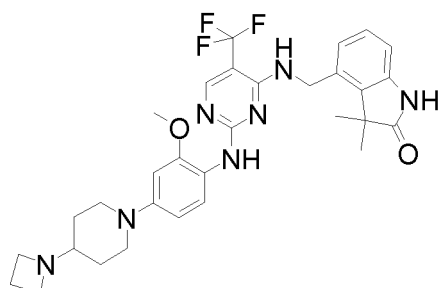
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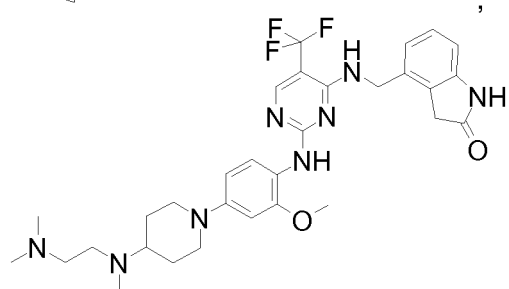
I-347



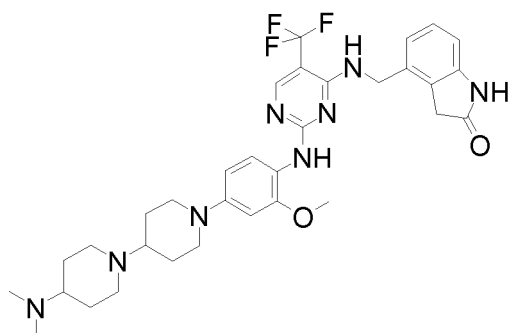
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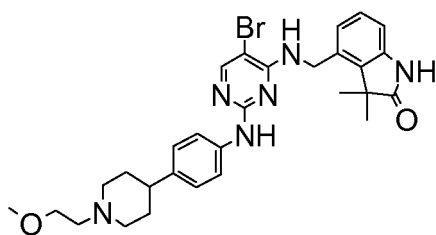
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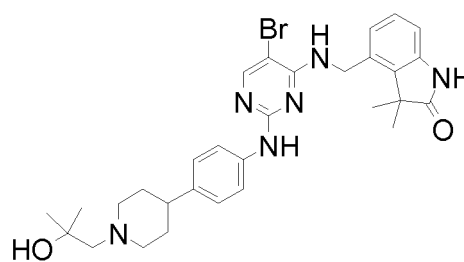
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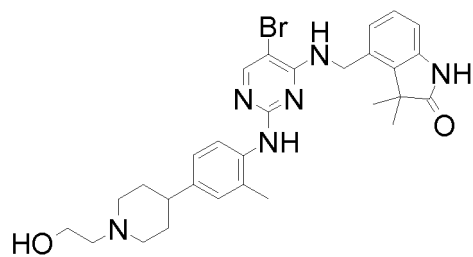
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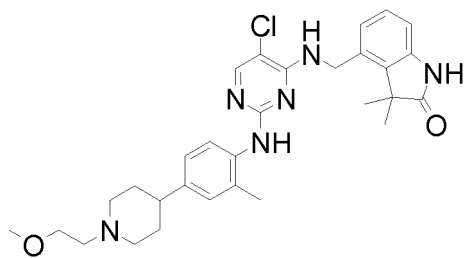
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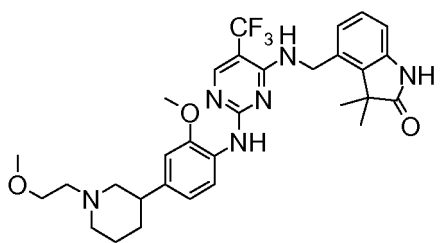
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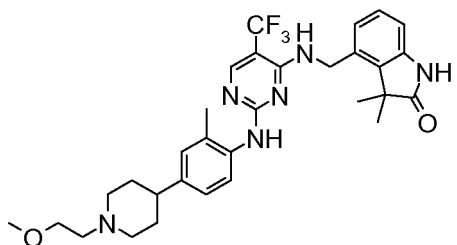
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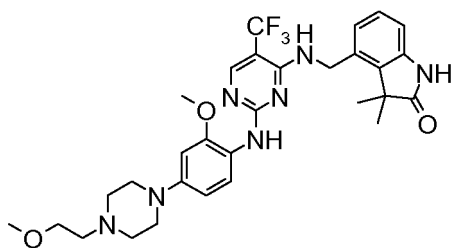
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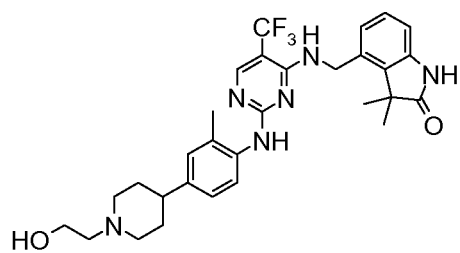
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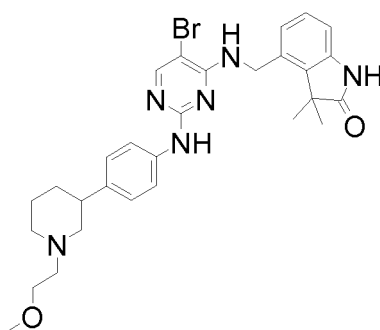
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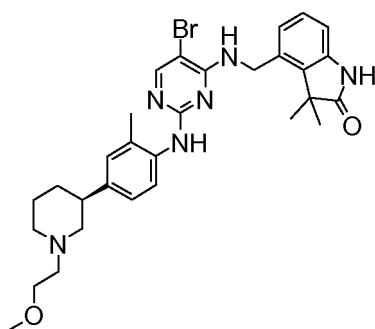
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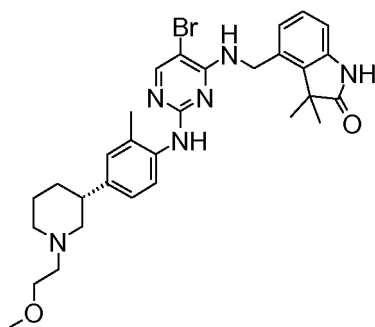
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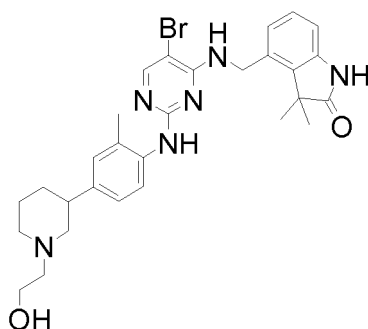
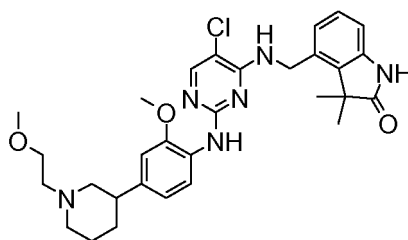
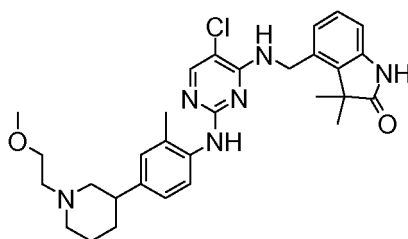


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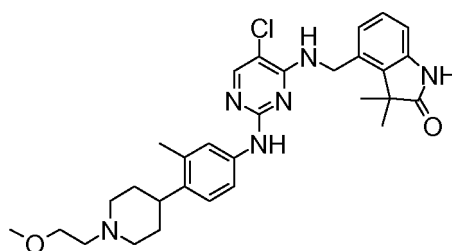


I-363



**I-364****I-371****I-373**

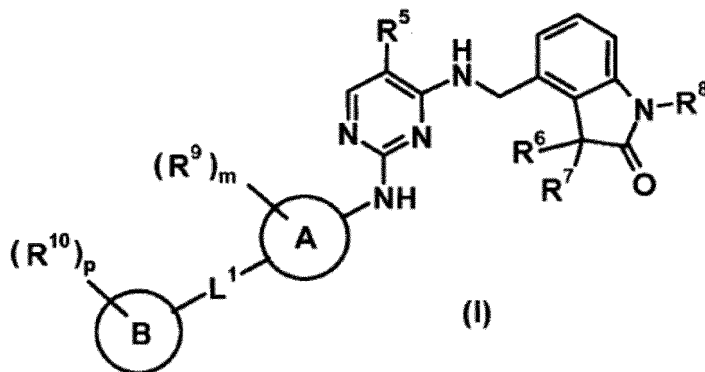
and

**I-376**

12. Verbindungen der allgemeinen Formel (I) nach einem der Ansprüche 1 bis 11 - oder die pharmazeutisch akzeptablen Salze davon - zur Verwendung als Arzneimittel.
13. Verbindungen der allgemeinen Formel (I) nach einem der Ansprüche 1 bis 11 - oder die pharmazeutisch akzeptablen Salze davon - zur Verwendung bei der Behandlung und/oder Prävention von Krebs, Infektionen, Entzündungen und Autoimmunerkrankungen.
14. Pharmazeutisches Präparat enthaltend als Wirkstoff eine oder mehrere Verbindungen der allgemeinen Formel (I) nach einem der Ansprüche 1 bis 11 - oder die pharmazeutisch akzeptablen Salze davon - gegebenenfalls in Kombination mit herkömmlichen Exzipienten und/oder Trägern.
15. Pharmazeutisches Präparat umfassend eine Verbindung der allgemeinen Formel (I) nach einem der Ansprüche 1 bis 11 - oder eines der pharmazeutisch akzeptablen Salze davon - und mindestens einen anderen zytostatischen oder zytotoxischen Wirkstoff, der von Formel (I) verschieden ist.

## Revendications

## 1. Composés de formule générale (I)



dans laquelle

R<sup>5</sup> est sélectionné parmi un groupe trifluorométhyle et un atome d'halogène ;

R<sup>6</sup>, R<sup>7</sup> et R<sup>8</sup> sont indépendamment sélectionnés dans chaque cas parmi un atome d'hydrogène et un groupe alkyle en C<sub>1-4</sub> ou

R<sup>6</sup> et R<sup>7</sup> conjointement à l'atome de carbone auquel ils sont liés forment un cycle hydrocarbure saturé à 3 à 5 chaînons ;

le système cyclique A est sélectionné parmi un groupe aryle en C<sub>6-10</sub>, un groupe hétérocyclyle à 3 à 14 chaînons et un groupe hétéroaryle à 5 à 12 chaînons ; chaque R<sup>9</sup> est indépendamment sélectionné dans chaque cas parmi un groupe alkyle en C<sub>1-6</sub>, un groupe haloalkyle en C<sub>1-6</sub>, un groupe alcoxy en C<sub>1-6</sub>, un groupe haloalcoxy en C<sub>1-6</sub>, un atome d'halogène et -CN ;

m représente 0, 1, 2 ou 3 ;

L<sup>1</sup> est sélectionné parmi une liaison, -(CH<sub>2</sub>)<sub>n</sub>-O-, -(CH<sub>2</sub>)<sub>n</sub>-NH-, -(CH<sub>2</sub>)<sub>n</sub>-NH-C(O)-, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-NH-, -(CH<sub>2</sub>)<sub>n</sub>- et -(CH<sub>2</sub>)<sub>n</sub>-C(O), alors que dans la présente nomenclature le groupe de liaison L<sup>1</sup> sur la droite se lie au système cyclique A ;

n représente 0, 1, 2 ou 3 ;

le système cyclique B est sélectionné parmi un groupe hétérocyclyle saturé ou insaturé à 4 à 10 chaînons et un groupe phényle ;

chaque R<sup>10</sup> est indépendamment sélectionné dans chaque cas parmi R<sup>a</sup> et R<sup>b</sup> ;

p représente 0, 1, 2 ou 3 ;

chaque R<sup>a</sup> représente indépendamment un groupe facultativement substitué par un ou plusieurs R<sup>b</sup> et/ou R<sup>c</sup> identiques ou différents sélectionnés parmi un groupe alkyle en C<sub>1-6</sub>, un groupe alcényle en C<sub>2-6</sub>, un groupe alcynyle en C<sub>2-6</sub>, un groupe cycloalkyle en C<sub>3-10</sub>, un groupe cycloalcényle en C<sub>4-10</sub>, un groupe aryle en C<sub>6-10</sub>, un groupe hétéroaryle à 5 à 12 chaînons et un groupe hétérocyclyle à 3 à 14 chaînons ;

chaque R<sup>b</sup> est indépendamment sélectionné dans chaque cas parmi -OR<sup>c</sup>, -SR<sup>c</sup>, -NR<sup>c</sup>R<sup>c</sup>, un atome d'halogène, -CN, -NO<sub>2</sub>, -C(O)R<sup>c</sup>, -C(O)OR<sup>c</sup>, -C(O)NR<sup>c</sup>R<sup>c</sup>, -C(NR<sup>f</sup>)NR<sup>c</sup>R<sup>c</sup>, -OC(O)R<sup>c</sup>, -OC(O)OR<sup>c</sup>, -S(O)<sub>2</sub>R<sup>c</sup>, -S(O)<sub>2</sub>NR<sup>c</sup>R<sup>c</sup>, -NR<sup>f</sup>C(O)R<sup>c</sup>, -NR<sup>f</sup>C(O)OR<sup>c</sup>, -NR<sup>f</sup>C(O)NR<sup>c</sup>R<sup>c</sup>, -NR<sup>f</sup>C(NR<sup>f</sup>)NR<sup>c</sup>R<sup>c</sup> et -NR<sup>f</sup>S(O)<sub>2</sub>R<sup>c</sup>, ainsi que le substituant bivalent =O, alors que ce dernier peut être uniquement un substituant dans des systèmes cycliques non aromatiques ;

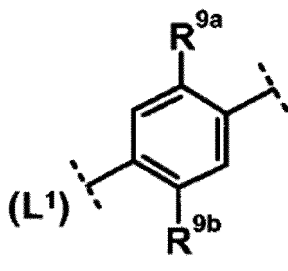
chaque R<sup>c</sup> représente indépendamment un atome d'hydrogène ou un groupe facultativement substitué par un ou plusieurs R<sup>d</sup> et/ou R<sup>e</sup> identiques ou différents sélectionnés parmi un groupe alkyle en C<sub>1-6</sub>, un groupe alcényle en C<sub>2-6</sub>, un groupe alcynyle en C<sub>2-6</sub>, un groupe cycloalkyle en C<sub>3-10</sub>, un groupe cycloalcényle en C<sub>4-10</sub>, un groupe aryle en C<sub>6-10</sub>, un groupe hétéroaryle à 5 à 12 chaînons et un groupe hétérocyclyle à 3 à 14 chaînons ; chaque R<sup>d</sup> est indépendamment sélectionné dans chaque cas parmi -OR<sup>e</sup>, -SR<sup>e</sup>, -NR<sup>e</sup>R<sup>e</sup>, un atome d'halogène, -CN, -NO<sub>2</sub>, -C(O)R<sup>e</sup>, -C(O)OR<sup>e</sup>, -C(O)NR<sup>e</sup>R<sup>e</sup>, -C(NR<sup>f</sup>)NR<sup>e</sup>R<sup>e</sup>, -OC(O)R<sup>e</sup>, -OC(O)OR<sup>e</sup>, -S(O)<sub>2</sub>R<sup>e</sup>, -S(O)<sub>2</sub>NR<sup>e</sup>R<sup>e</sup>, -NR<sup>f</sup>C(O)R<sup>e</sup>, -NR<sup>f</sup>C(O)OR<sup>e</sup>, -NR<sup>f</sup>C(O)NR<sup>e</sup>R<sup>e</sup>, -NR<sup>f</sup>C(NR<sup>f</sup>)NR<sup>e</sup>R<sup>e</sup> et -NR<sup>f</sup>S(O)<sub>2</sub>R<sup>e</sup>, ainsi que le substituant bivalent =O, alors que ce dernier peut être uniquement un substituant dans des systèmes cycliques non aromatiques ;

chaque R<sup>e</sup> représente indépendamment un atome d'hydrogène ou un groupe facultativement substitué par un ou plusieurs R<sup>f</sup> identiques ou différents sélectionnés parmi un groupe alkyle en C<sub>1-6</sub>, un groupe alcényle en C<sub>2-6</sub>, un groupe alcynyle en C<sub>2-6</sub>, un groupe cycloalkyle en C<sub>3-10</sub>, un groupe cycloalcényle en C<sub>4-10</sub>, un groupe

aryle en  $C_{6-10}$ , un groupe hétéroaryle à 5 à 12 chaînons et un groupe hétérocyclyle à 3 à 14 chaînons, et chaque  $R^f$  est indépendamment sélectionné dans chaque cas parmi un atome d'hydrogène et un groupe alkyle en  $C_{1-6}$ ,

alors que les composés (I) peuvent aussi facultativement survenir sous la forme de leurs tautomères, de leurs racémates, de leurs énantiomères, de leurs diastéréomères ou de mélanges de ceux-ci, ou comme les sels respectifs des formes susmentionnées.

2. Composés selon la revendication 1, dans lesquels le système cyclique A est sélectionné parmi un groupe phényle et un groupe hétéroaryle à 5 à 6 chaînons.
3. Composés selon l'une des revendications 1 et 2, dans lesquels m a la valeur de 0.
4. Composés selon l'une des revendications 1 et 2, dans lesquels m a la valeur de 1 ou 2 et  $R^9$  est sélectionné parmi un atome d'halogène, un groupe alkyle en  $C_{1-4}$  et un groupe alcoxy en  $C_{1-4}$ .
5. Composés selon l'une des revendications 1 à 4, dans lesquels le système cyclique A et les m groupes  $R^9$  représentent ensemble



$R^{9a}$  est sélectionné parmi un atome d'hydrogène, un groupe alkyle en  $C_{1-4}$  et un groupe alcoxy en  $C_{1-4}$  et  $R^{9b}$  est sélectionné parmi un atome d'hydrogène et un groupe alkyle en  $C_{1-4}$ .

6. Composés selon l'une des revendications 1 à 5, dans lesquels  $L^1$  est sélectionné parmi une liaison,  $-(CH_2)_2-O$ ,  $-NH-C(O)$ ,  $-C(O)-NH-$  et  $-C(O)$ , alors que dans la présente nomenclature le groupe de liaison  $L^1$  sur la droite se lie au système cyclique A.
7. Composés selon l'une des revendications 1 à 6, dans lesquels le système cyclique B est un groupe hétérocyclyle saturé ou insaturé, à 4 à 10 chaînons.
8. Composés selon l'une des revendications 1 à 7, dans lesquels p a la valeur de 0.
9. Composés selon l'une des revendications 1 à 7, dans lesquels p a la valeur de 1 ou 2, chaque  $R^{10}$  est indépendamment sélectionné dans chaque cas parmi  $R^a$  et  $R^b$  ; chaque  $R^a$  représente indépendamment un groupe facultativement substitué par un ou plusieurs  $R^b$  et/ou  $R^c$  identiques ou différents sélectionnés parmi un groupe alkyle en  $C_{1-6}$ , un groupe cycloalkyle en  $C_{3-10}$  et un groupe hétérocyclyle à 3 à 14 Chaînons ; chaque  $R^b$  est indépendamment sélectionné dans chaque cas parmi  $-OR^c$ ,  $-NR^cR^c$ , un atome d' halogène,  $-CN$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ ,  $-C(O)NR^cR^c$ ,  $-S(O)_2R^c$  et  $-S(O)_2NR^cR^c$ , ainsi que le substituant bivalent  $=O$ , alors que ce dernier peut être uniquement un substituant dans des systèmes cycliques non aromatiques ; chaque  $R^c$  représente indépendamment un atome d'hydrogène ou un groupe facultativement substitué par un ou plusieurs  $R^d$  et/ou  $R^e$  identiques ou différents sélectionnés parmi un groupe alkyle en  $C_{1-6}$ , un groupe cycloalkyle en  $C_{3-10}$ , un groupe hétéroaryle à 5 à 12 chaînons et un groupe hétérocyclyle à 3 à 14 Chaînons ; chaque  $R^d$  est indépendamment sélectionné dans chaque cas parmi  $-OR^e$ ,  $-NR^eR^e$ ,  $-CN$ ,  $-C(O)R^e$ ,  $-C(O)OR^e$  et  $-NR^fC(O)OR^e$ ,

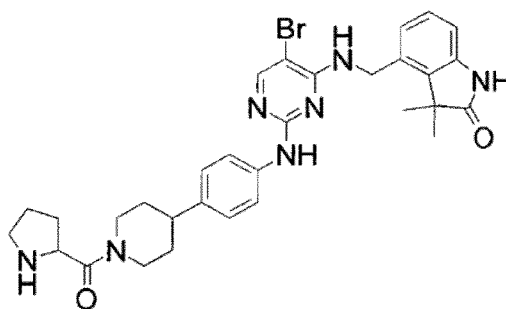
ainsi que le substituant bivalent =0, alors que ce dernier peut être uniquement un substituant dans des systèmes cycliques non aromatiques ;

chaque R<sup>e</sup> représente indépendamment un atome d'hydrogène ou un groupe facultativement substitué par un ou plusieurs R<sup>f</sup> identiques ou différents sélectionnés parmi un groupe alkyle en C<sub>1-6</sub>, un groupe aryle en C<sub>6-10</sub>, un groupe hétéroaryle à 5 à 12 chaînons et un groupe hétérocyclyle à 3 à 14 chaînons, et chaque R<sup>f</sup> est indépendamment sélectionné dans chaque cas parmi un atome d'hydrogène et un groupe alkyle en C<sub>1-6</sub>.

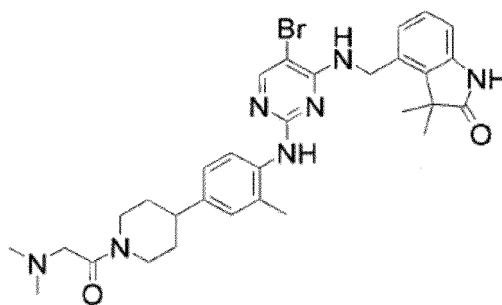
10. Composés selon l'une des revendications 1 et 9, dans lesquels p a la valeur de 1.

11. Composés selon la revendication 1, ou les sels pharmaceutiquement acceptables de ceux-ci, sélectionnés parmi :

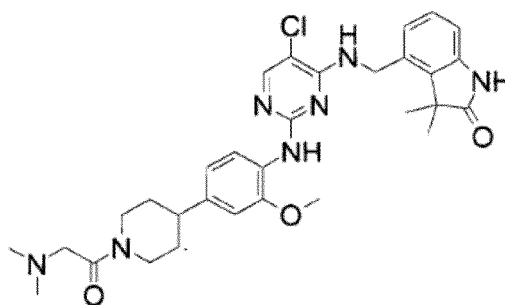
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I-57

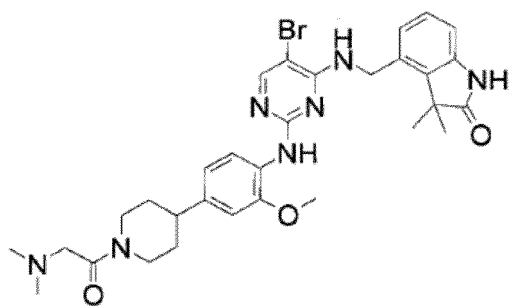


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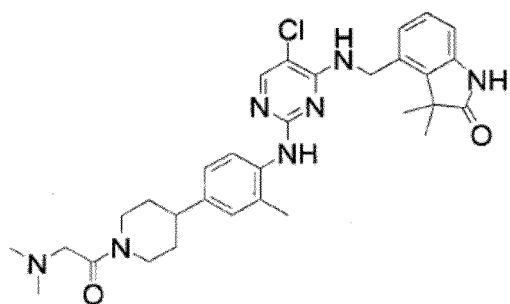




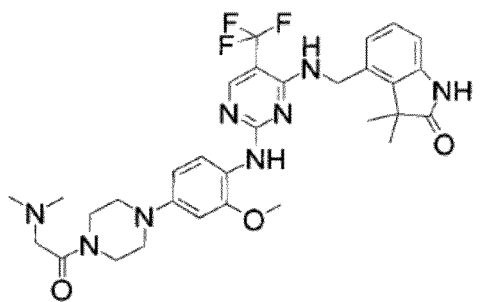
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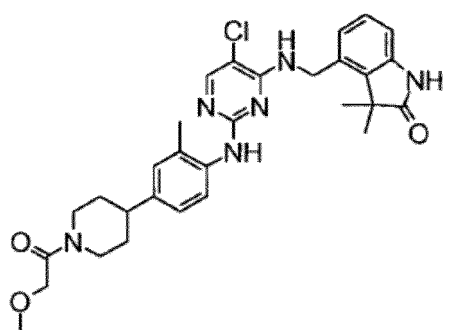
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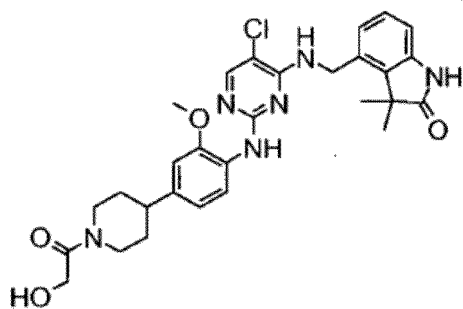
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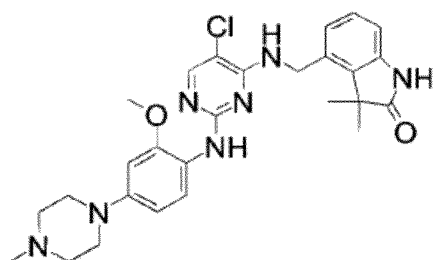
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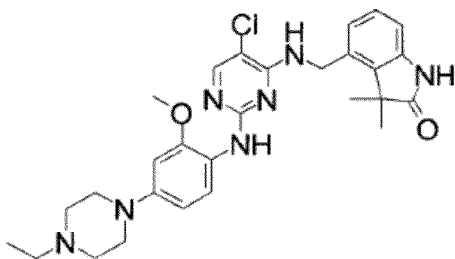
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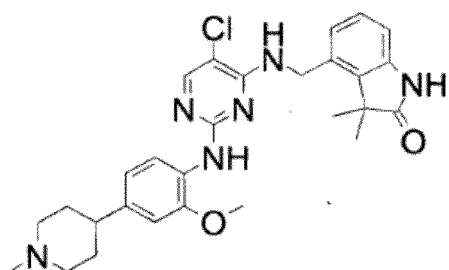
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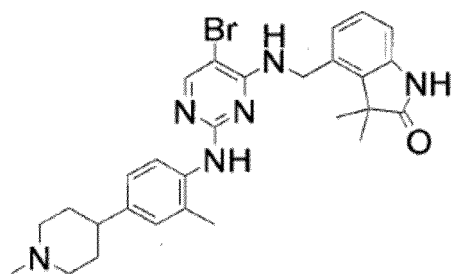
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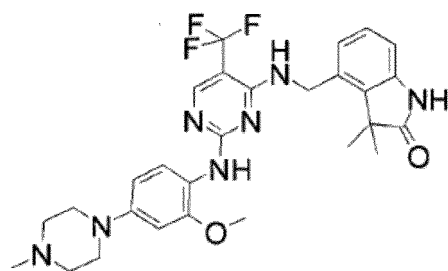
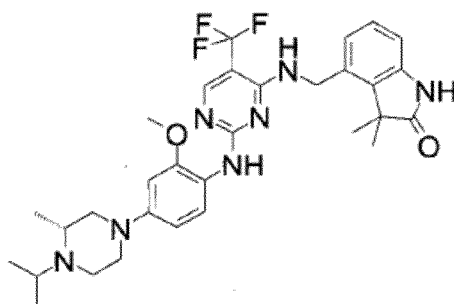
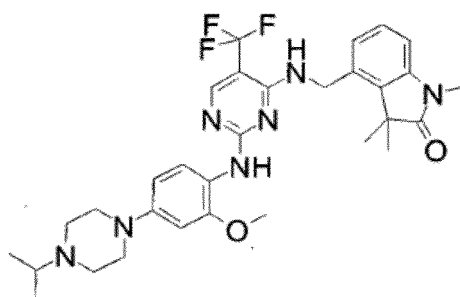
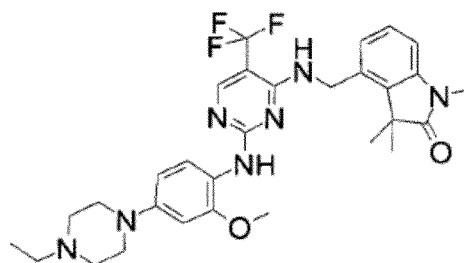
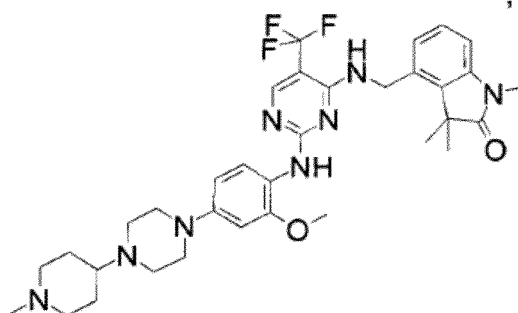


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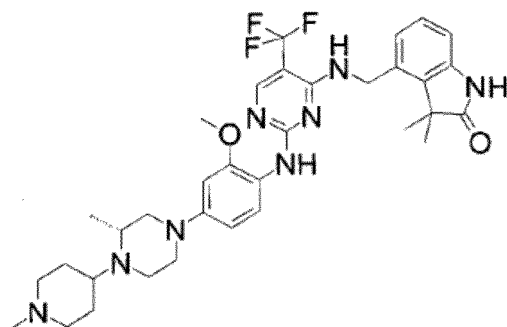


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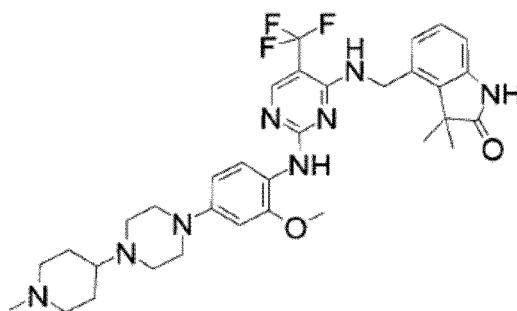


**I-104****I-106****I-128****I-129****I-130**

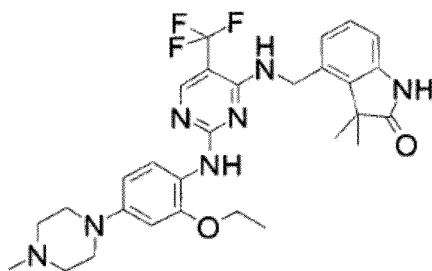
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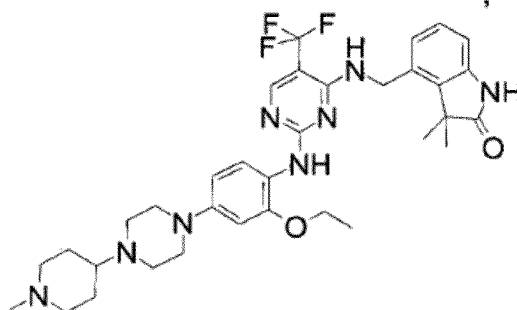
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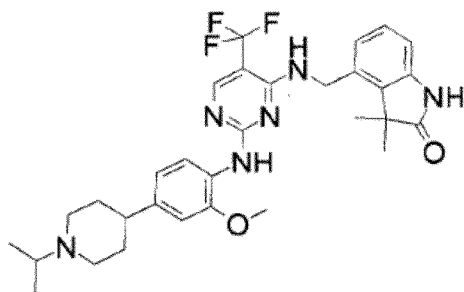
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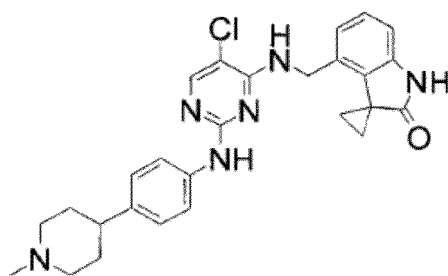
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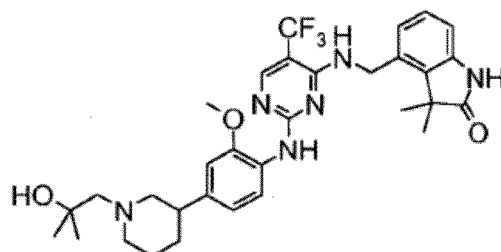
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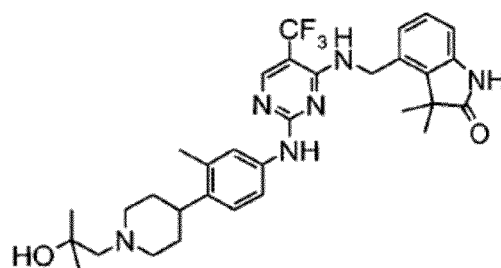
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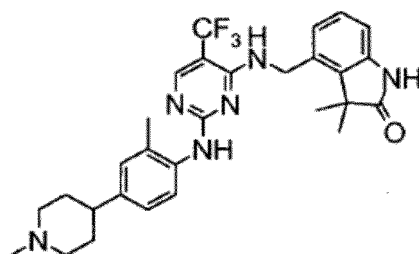
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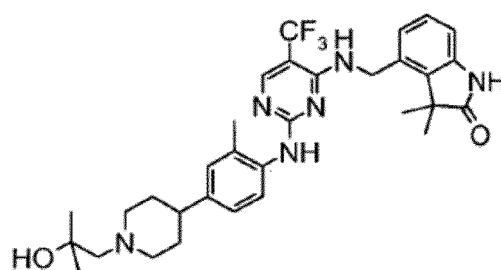
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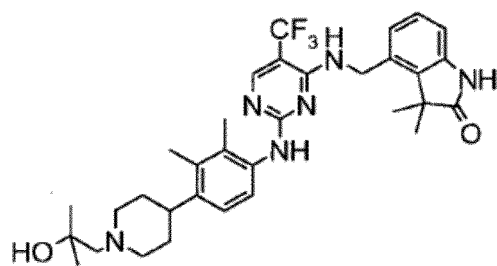
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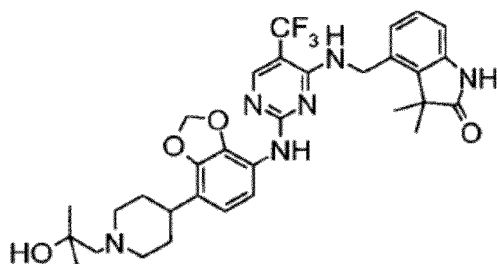
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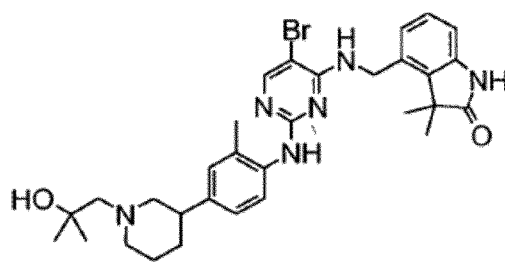
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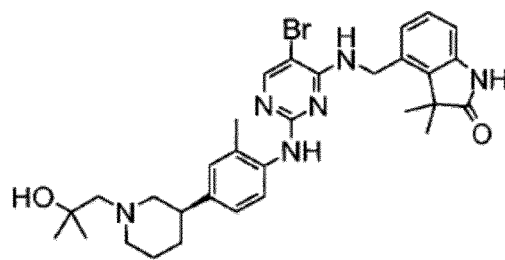
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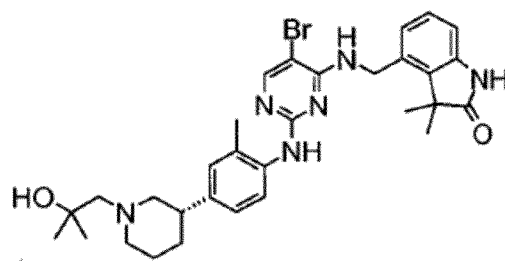
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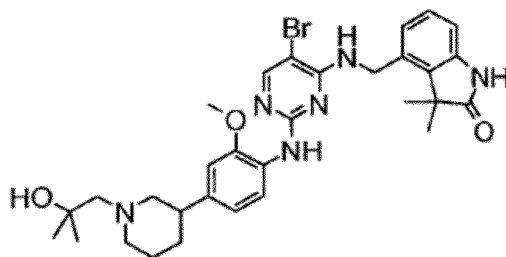
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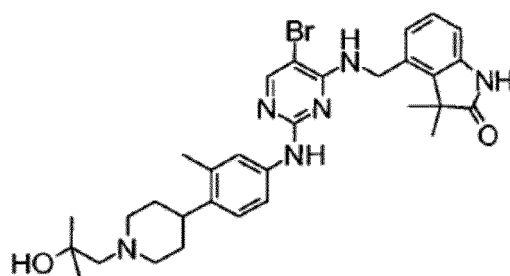
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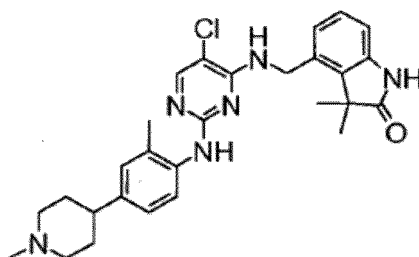
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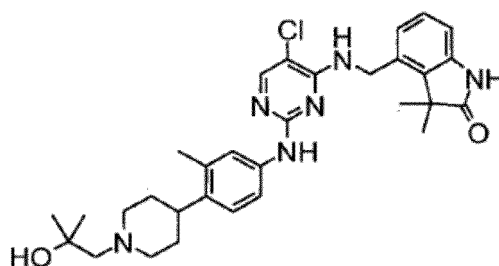
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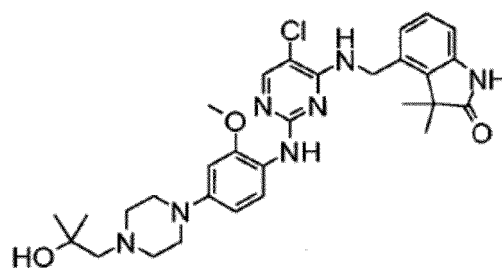
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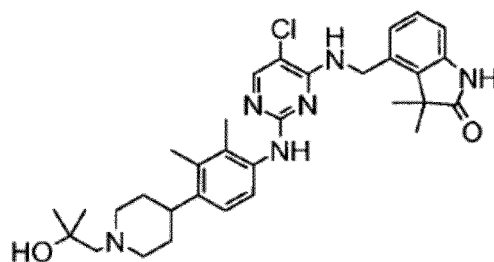
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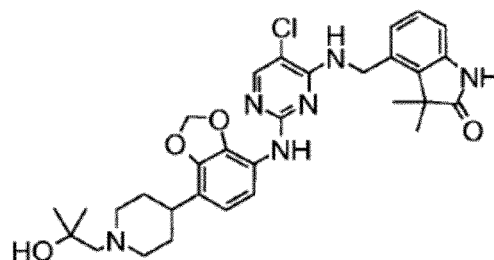
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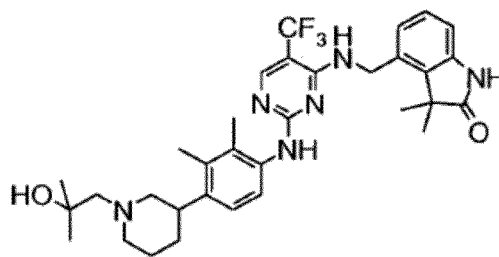
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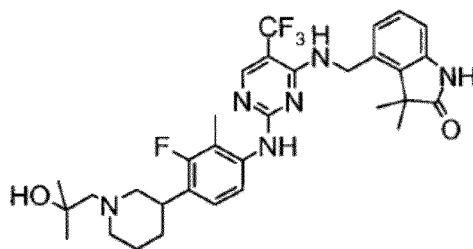
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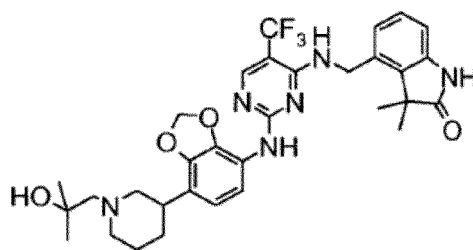
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I-345

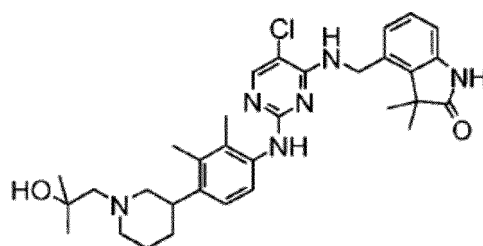


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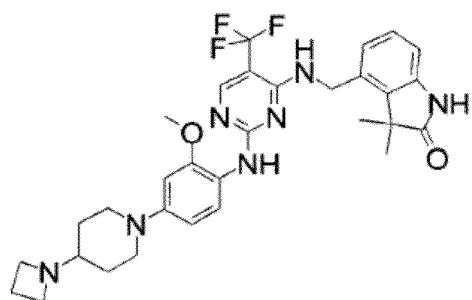




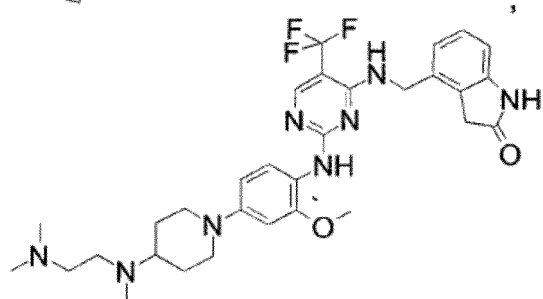
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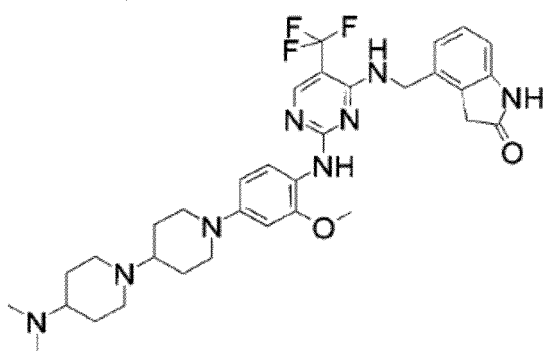
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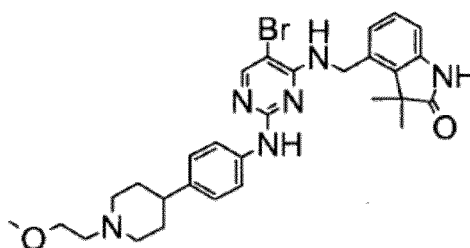
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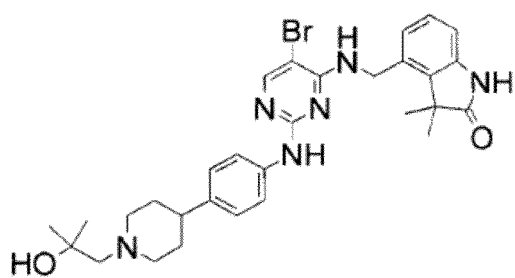
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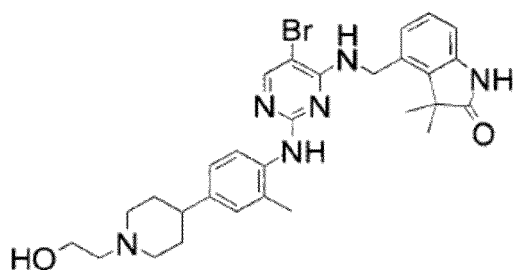
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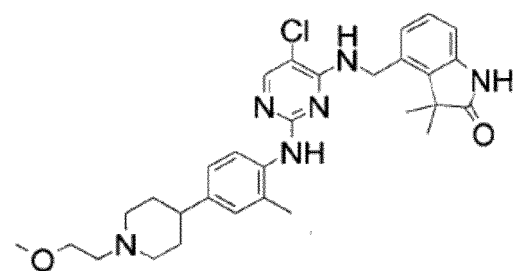
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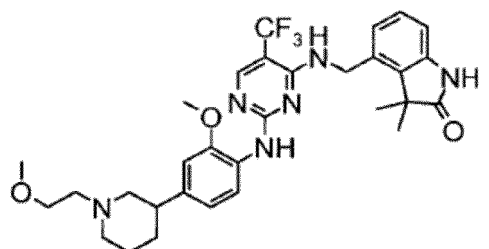
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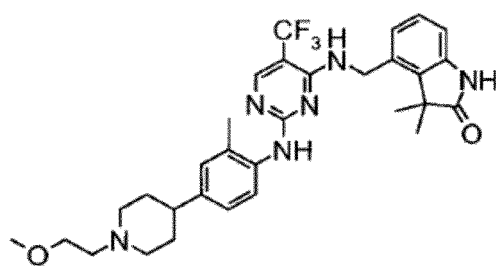
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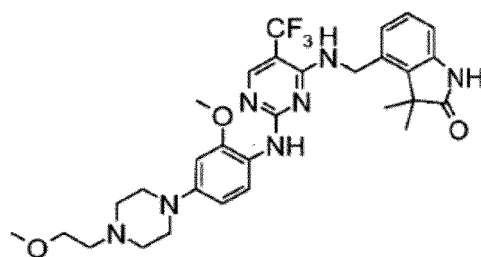
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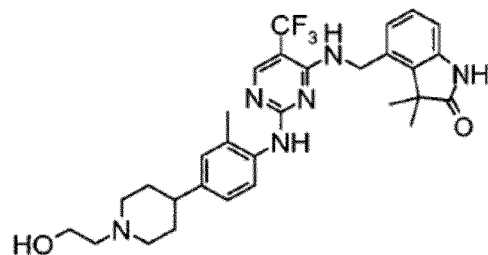
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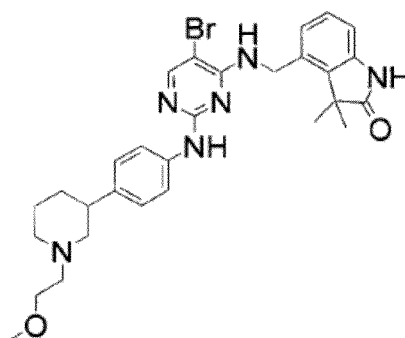
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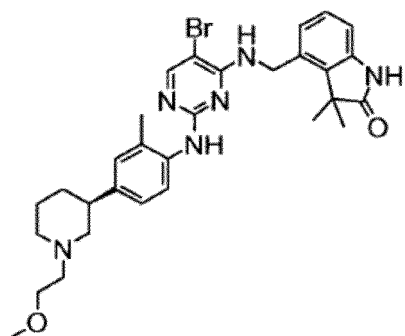
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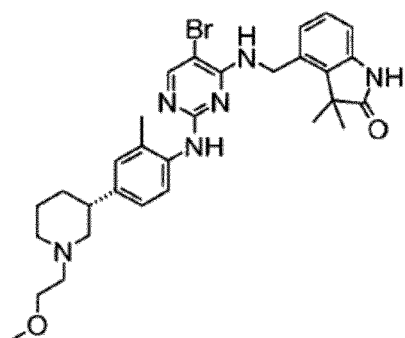
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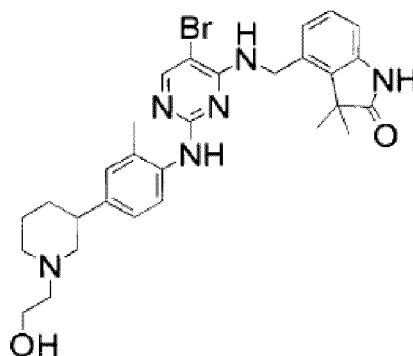
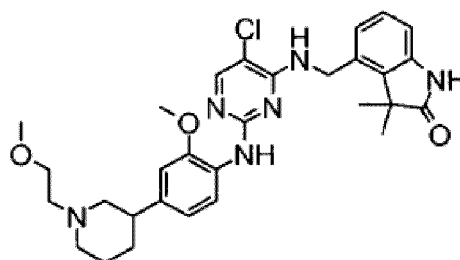
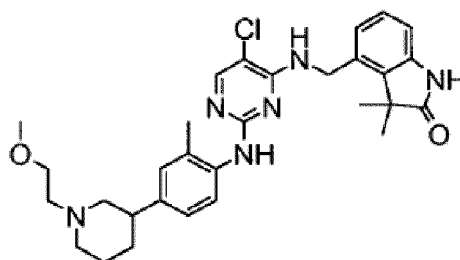


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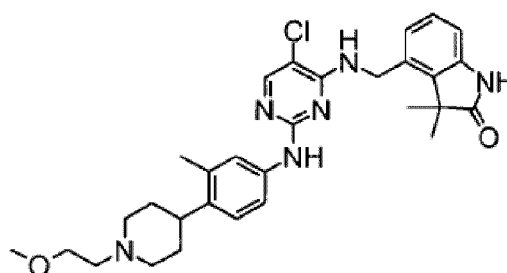


I-363



**I-364****I-371****I-373**

et

**I-376**

12. Composés de formule générale (I) selon l'une des revendications 1 à 11, ou leurs sels pharmaceutiquement acceptables, pour leur utilisation en tant que médicaments.
13. Composés de formule générale (I) selon l'une des revendications 1 à 11, ou leurs sels pharmaceutiquement acceptables, pour leur utilisation dans le traitement et/ou la prévention du cancer, des infections, des inflammations et des maladies auto-immunes.
14. Préparation pharmaceutique contenant en tant que substance active un ou plusieurs composés de formule générale (I) selon l'une des revendications 1 à 11, ou leurs sels pharmaceutiquement acceptables, facultativement en combinaison avec des excipients et/ou des véhicules classiques.

- 15.** Préparation pharmaceutique comprenant un composé de formule générale (I) selon l'une des revendications 1 à 11, ou l'un de ses sels pharmaceutiquement acceptables, et au moins une autre substance active cytostatique ou cytotoxique, différente de la formule (I).

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## REFERENCES CITED IN THE DESCRIPTION

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## Patent documents cited in the description

- WO 2006021544 A [0002]
- WO 2004080980 A [0003]
- WO 2002030927 A [0197]
- WO 2005023780 A [0208]
- WO 2006021548 A [0209]
- US 2008300242 A [0209]
- WO 2002006232 A [0209]
- WO 2005016894 A [0209]
- WO 2007115999 A [0209]

## Non-patent literature cited in the description

- **BIRGE, S.M. et al.** Pharmaceutical salts. *J. Pharm. Sci.*, 1977, vol. 66, 1-19 [0138]
- **HOFMANN, F. ; GARCIA-ECHEVERRIA, C. ; PICCI, P. ; SCOTLANDI, K.** Preclinical in vivo study of new insulin-like growth factor-I receptor--specific inhibitor in Ewing's sarcoma. *Clin. Cancer Res.*, 2007, vol. 13, 1322-1330 [0257]
- **PITTS, T.M. ; TAN, A.C. ; KULIKOWSKI, G.N. ; TENTLER, J.J. ; BROWN, A.M. ; FLANIGAN, S.A. ; LEONG, S. ; COLDREN, C.D. ; HIRSCH, F.R. ; VARELLA-GARCIA, M.** Development of an integrated genomic classifier for a novel agent in colorectal cancer: approach to individualized therapy in early development. *Clin Cancer Res.*, 2010, vol. 16, 3193-3204 [0257]
- **HALUSKA, P. ; CARBONI, J.M. ; LOEGERING, D.A. ; LEE, F.Y. ; WITTMAN, M. ; SAULNIER, M.G. ; FRENNESSON, D.B. ; KALLI, K.R. ; CONOVER, C.A. ; ATTAR, R.M.** In vitro and in vivo antitumor effects of the dual insulin-like growth factor-I/insulin receptor inhibitor, BMS-554417. *Cancer Res.*, 2006, vol. 66, 362-371 [0257]
- **GEORGII-HEMMING, P. ; WIKLUND, H.J. ; LJUNGGREN, O. ; NILSSON, K.** Insulin-like growth factor I is a growth and survival factor in human multiple myeloma cell lines. *Blood*, 1996, vol. 88, 2250-2258 [0257]
- **WAHNER HENDRICKSON, A.E. ; HALUSKA, P. ; SCHNEIDER, P.A. ; LOEGERING, D.A. ; PETERSON, K.L. ; ATTAR, R. ; SMITH, B.D. ; ERLICHMAN, C. ; GOTTARDIS, M. ; KARP, J.E.** Expression of insulin receptor isoform A and insulin-like growth factor-1 receptor in human acute myelogenous leukemia: effect of the dual-receptor inhibitor BMS-536924 in vitro. *Cancer Res.*, 2009, vol. 69, 7635-7643 [0257]